STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pegylated liposomal irinotecan hydrochloride trihydrate for treating pancreatic cancer after gemcitabine [ID778]

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This report was commissioned by the NIHR HTA Programme as project number 15/121/02

Completed 1st July 2016

CONTAINS ACADEMIC AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Pegylated liposomal irinotecan hydrochloride trihydrate for treating pancreatic cancer after gemcitabine [ID778]

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Date completed: 1st July 2016

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 15/121/02.

Declared competing interests of the authors: None.

Acknowledgements: The authors thank Juliet Hounsome, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool, who assisted with data extraction of trials for Section 4.7 of this ERG report. The authors also thank Dr Pauline Leonard, Consultant Medical Oncologist, Whittington Hospital and Janette Greenhalgh, Senior Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool, for comments on the final draft of this report.

Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Fleeman N, Abdulla A, Bagust A, Beale S, Richardson M, Stainthorpe A, Boland A, Kotas E, McEntee J, Palmer D. Pegylated liposomal irinotecan hydrochloride trihydrate for treating pancreatic cancer after gemcitabine [ID778]: A Single Technology Appraisal. LR*i*G, University of Liverpool, 2016.

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Richardson M	Critical appraisal of the statistical evidence
Stainthorpe A	Summary and critical appraisal of economic evidence
Boland A	Critical appraisal of the clinical and economic evidence, editorial input
Kotas E	Critical appraisal of the database searching
McEntee J	Critical appraisal of the submission
Palmer D	Clinical advice and critical appraisal of the clinical sections of the company submission

All authors read and commented on draft versions of the ERG report.

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LIST OF ABBREVIATIONS

5-FU	5-fluorouracil
AE	adverse event
ASCO	American Society of Clinical Oncology
BSA	body surface area
CA19-9	cancer antigen 19-9
CHMP	Committee for Human Medicinal Products
CI	confidence interval
CS	company submission
CSR	clinical study report
ECOG	Eastern Cooperative Oncology Group
eMIT	Electronic Market Information Tool
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
EQ-5D	EuroQol-5 dimension
ERG	Evidence Review Group
FOLFIRINOX	folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan plus oxaliplatin
FOLFIRI	folinic acid (leucovorin) plus 5- fluorouracil plus irinotecan
FOLFOX	folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin
H-H	cumulative hazard versus cumulative hazard
HR	hazard ratio
HRQoL	health related quality of life
ICER	incremental cost-effectiveness ratio
ITC	indirect treatment comparison
ITT	intention-to-treat
IVRS	interactive voice recognition system

K-M	Kaplan-Meier
KOLS	key opinion leaders
KPS	Karnofsky performance status
LV	leucovorin
LY	life year
Nal-iri	pegylated liposomal irinotecan hydrochloride trihydrate
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
OFF	oxaliplatin plus folinic acid (leucovorin) plus 5-fluorouracil
ORR	objective response rate
OS	overall survival
PAS	Patient Access Scheme
PFS	progression-free survival
PH	proportional hazards
PS	performance status
PSA	probabilistic sensitivity analysis
QALY	quality adjusted life year
Q-TWiST	quality adjusted time without symptoms or toxicity
RECIST	response evaluation criteria in solid tumours
SmPC	summary of product characteristics
TSAP	trial statistical analysis plan
STA	single technology appraisal
TEAE	treatment-emergent adverse event
TR-TEAE	treatment-related treatment-emergent adverse event
TTF	time to treatment failure

1 SUMMARY

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence has been submitted to NICE by Baxalta in support of the use of pegylated liposomal irinotecan hydrochloride trihydrate (Onivyde^{TM}) (hereafter referred to as nal-iri) for use within its anticipated marketing authorisation, i.e. in combination with 5-fluorouracil (5-FU) and folinic acid (also known as leucovorin [LV]) for the treatment of metastatic adenocarcinoma of the pancreas, in adult patients who have progressed following gemcitabine-based therapy.

1.1 Critique of the decision problem in the company submission

The decision problem addressed by the company is similar to the decision problem described in the final scope issued by NICE. Reflecting the anticipated licensed indication for nal-iri+5-FU/LV, the population of interest is adult patients with metastatic adenocarcinoma of the pancreas who have progressed following gemcitabine-basedtherapy. The main difference between the two decision problems is the stated range of comparators. The final scope lists the following comparators:

- oxaliplatin in combination with fluorouracil and folinic acid (oxaliplatin+5-FU/LV),
- oxaliplatin in combination with capecitabine (oxaliplatin+capecitabine)
- fluoropyrimidine monotherapy (e.g. capecitabine or 5-FU).

Evidence provided by the company and clinical advice to the ERG suggest that in the NHS, oxaliplatin+5-FU/LV is the treatment most often given to treat patients with metastatic adenocarcinoma of the pancreas who have progressed following gemcitabine-based chemotherapy (approximately 75% of cases). Oxaliplatin+5-FU/LV is administered in one of three formulations: mFOLFOX6, mFOLFOX4 or OFF. The former two regimens are most frequently used and the specifics of the regimen (and the extent to which it is used) vary by geographical area. Capecitabine monotherapy and oxaliplatin+capecitabine are less frequently used treatment alternatives and 5-FU/LV monotherapy is only rarely used, if at all. The company has only provided evidence for the clinical effectiveness of nal-iri+5-FU/LV versus 5-FU/LV.

The company explored the feasibility of an indirect treatment comparison (ITC) to compare the effectiveness of nal-iri+5-FU/LV with the other comparators detailed in the final scope

issued by NICE. Outputs from these analyses were used in the company model to generate cost effectiveness results for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company conducted a systematic review to identify randomised controlled trials (RCTs) and non-randomised studies (including observational studies) investigating the effectiveness of nal-iri+5-FU/LV and/or comparators relevant to the decision problem. The company identified 13 RCTs and 15 non-randomised studies. Only one RCT was considered directly relevant to the decision problem: the NAPOLI-1 trial.

The NAPOLI-1 trial was a multinational phase III open-label RCT comparing the efficacy and safety of nal-iri+5-FU/LV versus 5-FU/LV and also nal-iri monotherapy versus 5-FU/LV in patients with metastatic pancreatic cancer previously treated with gemcitabine-based therapy. Only the former comparison is relevant to the decision problem and only these results are reported in the company submission (CS), although safety data from the nal-iri monotherapy arm are also presented. Randomisation was stratified according to baseline albumin levels (≥4.0 g/dL versus <4.0 g/dL), Karnofsky performance score (KPS) (70 and 80 versus ≥90), and ethnicity (Caucasian versus East Asian versus all others). The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), time to treatment failure (TTF), objective response rate (ORR), tumour marker response, clinical benefit rate (CBR), adverse events (AEs) and health related quality of life (HRQoL). The primary analysis was performed using data from the 14 February 2014 data cut. The primary population for OS, PF, TTF and ORR was the intention-to-treat (ITT) population. According to the company's risk of bias assessment, the NAPOLI-1 trial was of reasonable quality.

Results from the primary analysis of NAPOLI-1 trial data (n=236) show that median OS was longer for patients in the nal-iri+5-FU/LV arm than for patients in the 5-FU/LV arm (6.1 months versus 4.2 months). The difference was statistically significant (hazard ratio [HR] 0.67; 95% confidence interval [CI] 0.49 to 0.92; p=0.0122). Results from subgroup analyses suggest that the treatment effect [redacted] nal-iri+5-FU/LV [redacted] 5-FU/LV [redacted]. Median PFS was longer for patients treated with nal-iri+5-FU/LV than for patients treated with 5-FU/LV (3.1 months versus 1.5 months). The difference was statistically significant (HR 0.56; 95% CI 0.41 to 0.75; p=0.0001). Sensitivity analyses included, but were not limited to, generating results for the per protocol (PP) population. The PP population consisted of patients who received treatment for at least 6 weeks and did not violate any inclusion/exclusion criteria nor

significantly deviate from the protocol, including significant deviations in study drug administration. The company also presented median OS and median PFS results for the ITT population generated from analyses of final data cut (March 2016) data; these results are [redacted] to the interim results presented in the CS.

Safety results are reported in the CS for the safety population (n=251), i.e. patients who received at least one dose (including partial dose) of study medication. In the nal-iri arm, the incidence of AEs was higher than in the 5-FU/LV arm. For patients treated with nal-iri+5-FU/LV the primary reason for dose delay was myelosuppression (e.g. neutropenia), the main reasons for dose reductions were myelosuppression and gastrointestinal disorders and the primary reasons for discontinuation of treatment were gastrointestinal disorders, and infections and infestations.

The primary health related quality of life evidence was derived from the patient-reported outcomes (PRO) population, which only included ITT patients who had completed the EORTC-QLC-C30 questionnaire at baseline and on at least one subsequent occasion ([redacted]). No statistically significant differences were reported between arms in scores at 6 or 12 weeks; comparative EORTC-QLC-C30 data after 12 weeks were not reported. The company also undertook a quality adjusted time without symptoms or toxicity (Q-TWiST) analysis for the ITT population (n=236). The company states that the results from the Q-TWiST analysis (relative Q-TWiST gain of 24%) show that treatment with nal-iri+5-FU/LV results in statistically significant and clinically important gains in quality-adjusted survival compared with treatment with 5-FU/LV. The company reported that a sensitivity analysis conducted in the PP population supported this finding.

The company explored the feasibility of conducting a network meta-analysis (NMA) or ITC to compare nal-iri+5-FU/LV with other relevant comparators (e.g. oxaliplatin+5-FU/LV). The company considered a network of evidence formed by 12 of the 13 RCTs included in its systematic review and presented network diagrams summarising the identified evidence. Three trials could be linked by a common comparator (5-FU/LV): the NAPOLI-1 trial, CONKO-003 trial and PANCREOX trial. The company stated that the proportional hazards (PH) assumptions necessary to generate reliable results were violated for both OS and PFS. In addition, the company considered that trials were too heterogeneous in terms of trial location, patient characteristics, prior treatment with gemcitabine (monotherapy versus combination therapy) and length of trial follow-up for results to be used in an ITC. These limitations led the company to conclude that an ITC was “unfeasible”. Advice, sought by the company, from a panel of three UK key opinion leaders (KOLS) was that it was difficult to

compare the key trials and combining data from them in an ITC might be considered flawed and “naïve”.

Evidence from one phase II non-RCT (NCT00813163) is also presented in the CS, including safety data. This non-randomised study was not included in the company’s systematic review because it only investigated the effectiveness of nal-iri monotherapy. The company states that results from this study show that, overall, the safety profiles of nal-iri+5-FU/LV and nal-iri monotherapy in the NAPOLI-1 trial were consistent with prior experience (i.e. consistent with the results of this study (NCT00813163).

1.3 Summary of the ERG’s critique of clinical effectiveness evidence submitted

The ERG is not aware of any additional RCTs or non-randomised studies that the company should have included as part of the evidence base.

Overall, the ERG agrees with the company that the NAPOLI-1 trial is of reasonable quality, although there is a risk of bias arising from the fact that it was an open-label trial. This may explain why a greater proportion of patients withdrew from the 5-FU/LV arm (10.9%) before treatment than from the nal-iri+5-FU/LV arm (1.7%). The open-label nature of the trial, combined with a lack of independent assessment of disease progression, may also have introduced bias into the assessment of disease progression, favouring nal-iri+5-FU/LV over 5-FU/LV.

Despite slight differences in some baseline characteristics, the ERG is satisfied that the treatment groups in the NAPOLI-1 trial were relatively well balanced. The patient population in the NAPOLI-1 trial was generally similar to the population that is likely to be considered for treatment with nal-iri+5-FU/LV in NHS clinical practice in England, aside from the usual caveat that only suitably fit patients are recruited to clinical trials which means the trial population may be slightly younger and fitter than the population seen in clinical practice.

The ERG is generally satisfied with the statistical approach employed by the company to analyse the data from the NAPOLI-1 trial, with the exception that the results of formal testing of PH for OS, PFS and TTF were not presented in the CS. The ERG’s own analyses show that the assumptions of PH for OS, PFS and TTF in the nal-iri+5-FU/LV and 5-FU/LV arms are not supported and, therefore, the log-rank test results that the company uses to demonstrate statistical significance in terms of median OS, PFS and TTF are not valid.

While the company states that the results of the sensitivity analyses support the primary analyses, the ERG notes that the analyses of data from the PP population generated median

OS and PFS results that were longer (in both treatment arms) than those for the ITT population (OS: 8.9 versus 5.1 months; PFS: 4.3 versus 1.6 months). However, the number of patients in the PP population was relatively small, indicating that only 56% of the nal-iri+5-FU/LV arm (66/117 patients) and 60% of the 5-FU/LV arm (71/117) received treatment for at least 6 weeks and did not violate any inclusion/exclusion criteria nor significantly deviate from the protocol. The most common reason for exclusion from the PP population was "insufficient dosing" or receiving no dose of the study drug. Thus patients in the NAPOLI-1 trial may have experienced considerably more treatment benefit had they been able to receive at least 80% of the planned dose throughout the duration of the study, particularly in the nal-iri+5-FU/LV arm.

Whilst, theoretically, HRQoL data from the NAPOLI-1 trial is useful, the ERG questions whether the EORTC-QLQ-C30 questionnaire results can be considered robust, given the relatively small number of patient responses. The ERG agrees that the Q-TWiST score of 24% suggests a clinically important result. However, the ERG cautions that the Q-TWiST analysis was not presented in the Clinical Study Report (CSR) of the NAPOLI-1 trial and so appears to be a post-hoc exploratory analysis; the findings should therefore be treated with caution.

Despite some apparent differences in the incidence rates of some AEs for patients treated with nal-iri monotherapy in the NAPOLI-1 trial compared with those in the NCT00813163 study, the ERG generally agrees with the company's overall assessment that the safety profiles of nal-iri+5-FU/LV and nal-iri monotherapy are consistent with prior experience with nal-iri, non-liposomal irinotecan and 5-FU.

Regarding the feasibility of conducting an ITC to allow the efficacy of nal-iri+5-FU/LV to be compared with that of other relevant comparators, the ERG agrees with the company that trial heterogeneity is a limitation. However, the ERG's primary reason for rejecting the validity of the results from the ITC relate to the PH assumptions being violated both within and between the arms of the three trials included in the ITC (i.e. the NAPOLI-1, CONKO-003 and PANCREOX trials) for both OS and PFS data. Thus the ERG considers that it is not possible to derive a credible estimate of clinical or cost effectiveness for nal-iri+5-FU/LV compared with oxaliplatin+5-FU/LV.

To enable a crude comparison of efficacy and safety data across key RCTs, the ERG extracted relevant data from RCTs of oxaliplatin+5-FU/LV that were identified in the company's systematic review (i.e. the CONKO-003, PANCREOX, SWOG S1115 and Yoo trials). Overall, the PFS and OS outcomes for patients treated with oxaliplatin+5-FU/LV

reported in these trials are similar in magnitude to the PFS and OS outcomes of patients who were treated with nal-iri+5-FU/LV in the NAPOLI-1 trial. Neutropenia is recognised as a very common AE for patients treated with nal-iri+5-FU/LV, this AE appears to be even more common in patients receiving oxaliplatin+5-FU/LV, and the same is true of the incidence of neurotoxicity. The proportion of patients with grade 3 to 4 neutropenia reported with mFOLFOX6 in the PANCREOX trial was 32.7% compared with 14.5% with nal-iri+5-FU/LV (14.5%) in the NAPOLI-1 trial. Grade ≥3 peripheral neuropathy was reported to be ~4% with the OFF and mFOLFOX6 without 5-FU bolus regimens in the CONKO-003 and SWOG S1115 trials but there were no cases of grade ≥3 peripheral neuropathy (a common neurotoxicity) with nal-ire+5-FU/LV in the NAPOLI-1 trial. Diarrhoea, on the other hand, appears to be more common for patients treated with nal-iri+5-FU/LV than for patients receiving oxaliplatin+5-FU/LV; grade ≥3 diarrhoea was 12.8% with nal-iri+5-FU/LV in the NAPOLI-1 trial, compared with no more than 6.5% with mFOLFOX6 without bolus 5-FU in the SWOG S1115 trial. The ERG urges caution in interpreting the findings from these crude comparisons due to potential differences in the trial populations and advises that they should be considered, at best, to be exploratory.

1.4 Summary of submitted cost effectiveness evidence

The company developed a de novo partitioned survival model in Microsoft Excel to compare the cost effectiveness of treatment with nal-iri+5-FU/LV with (i) oxaliplatin+5-FU/LV (NHS standard care) and (ii) 5-FU/LV (company base case). The model comprised four mutually exclusive health states: pre-progression on treatment, pre-progression off treatment, post-progression treatment (including patients receiving second-line therapy and those receiving palliative care) and death. All patients enter the model in the pre-progression on treatment health state. The model time horizon set at 10 years with a 1-week cycle length. The model perspective was that of the UK NHS. Outcomes were measured in quality adjusted life years (QALYs), and both costs and QALYs discounted at an annual rate of 3.5%, as recommended by NICE. Survival for patients treated with nal-iri+5-FU/LV and those treated with 5-FU/LV was estimated based on data from the NAPOLI-1 trial. Survival for patients treated with oxaliplatin+5-FU/LV was based on data from the company's ITC. Utility values were taken from a previous NICE STA (nab-paclitaxel in combination with gemcitabine for previously untreated metastatic pancreatic cancer [TA360]). Resource use and costs were estimated based on information from the NAPOLI-1 trial, published sources and clinical experts.

The company's (corrected) incremental cost effectiveness ratio (ICER) for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV is £[redacted] per QALY gained and the ICER for

the comparison of nal-iri+5-FU/LV versus 5-FU/LV is £[redacted] per QALY gained. The company did not provide any deterministic sensitivity analyses for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV, but one-way sensitivity analyses were conducted for the comparison of nal-iri+5-FU/LV versus 5-FU/LV. The company base case ICER per QALY gained for nal-iri+5-FU/LV versus 5-FU/LV was most sensitive to varying the pre-progression utility values. The results were also sensitive to the cost of nal-iri and to mean body surface area (BSA).

The company conducted probabilistic sensitivity analyses (PSAs). The (corrected) ICER from the PSA for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV is £[redacted] per QALY gained. The company's (corrected) probabilistic ICER for the comparison of nal-iri+5-FU/LV versus 5-FU/LV is £[redacted] per QALY gained. At a cost effectiveness threshold of £50,000 per QALY gained, treatment with nal-iri+5-FU/LV has a [redacted]% probability of being cost effective compared with treatment with oxaliplatin+5-FU/LV or with 5-FU/LV.

The company carried out three scenario analyses comparing nal-iri+5-FU/LV with oxaliplatin+5-FU/LV and with 5-FU/LV. The resultant (uncorrected) ICERs per QALY gained for treatment with nal-iri+5-FU/LV versus treatment with oxaliplatin+5-FU/LV varied from £[redacted] (AE utility decrements omitted) to £[redacted] (using data from the February 2014 data cut from the NAPOLI-1 trial with a log-normal distribution for modelling time-to-event data). The ICERs per QALY gained for the comparison of treatment with nal-iri+5-FU/LV versus treatment with 5-FU/LV varied from £[redacted] (AE utility decrements omitted) to £[redacted] (using log-logistic rather than log-normal distribution for modelling time-to-event data).

1.5 Summary of the ERG's critique of cost effectiveness evidence

The company's decision analytic model is structured appropriately according to conventional practice. An error was detected in the model with regards to the health state utility value for the post-progression health state resulting in an amendment in the base case ICER per QALY gained estimate to £[redacted]. The ERG identified several areas of the concern within the cost effectiveness analysis, namely: (i) the ITC for the nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV comparison (ii) the use of time to event data from the NAPOLI-1 trial, (iii) drug costing and (iv) use of inappropriate health state utility values.

The ERG considers the company's base case ICER for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV to be unreliable due to the use of an invalid ITC. Furthermore, the company's use of the PH assumption is inappropriate since log-normal models are accelerated failure-time models. The ERG conducted a scenario analyses to aid decision

making; the results suggest that any interpretation surrounding the ICER estimate should be made with caution.

The ERG questions the company's use of the log-normal parametric curves to reflect patient survival rather than the mature K-M data from the NAPOLI-1 trial for the nal-iri+5-FU/LV and 5-FU/LV treatment arms. The ERG notes that the use of the K-M data from the NAPOLI-1 trial reduces the mean survival gain for nal-iri+5-FU/LV versus 5-FU/LV from 2.5 to 1.67 months. The company's approach to modelling survival data therefore overestimates the OS of nal-iri+5-FU/LV and underestimates the overall ICER per QALY gained estimate for nal-iri+5-FU/LV versus 5-FU/LV.

In the company model it is assumed that the pre-progression time on treatment for oxaliplatin+5-FU/LV is equivalent to nal-iri+5-FU/LV. This assumption results in the proportion of patients on treatment in the pre-progression on treatment state to exceed the proportion of patients in the PFS state. The requirement of a correction in the company model to prevent this suggests that the company's approach has no logical basis.

The ERG considers several issues attributable to treatment costs in the company model to be unrepresentative of clinical practice in the UK. These include dosing intensity adjustments, undifferentiated BSA calculations (relevant to dosing), drug acquisition costs which do not take into account the availability of generic drug costs or different vial sizes, and the assumption that, in NHS clinical practice, patients are likely to receive further chemotherapy following the failure of second-line treatment.

The ERG also considers the utility values used in the company model to be an overestimate of patient HRQoL. The utility values were obtained from the ERG report for the appraisal of nab-paclitaxel in combination with gemcitabine for previously untreated metastatic pancreatic cancer in a first-line patient population (TA360). The ERG notes that alternative utility values are available that better reflect the target population. Furthermore, the ERG also considers that terminal disutility should have been accounted for in the company model.

1.6 Summary of company's case for end of life criteria being met

The company has put forward a case that nal-iri+5-FU/LV meets the NICE's End of Life criteria. The company states that nal-iri+5-FU/LV will be indicated for patients with a short life expectancy, normally less than 24 months and for a small patient population (10-year prevalence of pancreatic cancer in the UK in 2006 was 4349). The company considers that while the 1.9 month gain in median OS reported in the NAPOLI-1 trial for nal-iri+5-FU/LV compared with 5-FU/LV does not meet the 3 month OS gain stipulated in the End Of Life

guidance criteria, it represents a 45% increase in OS that would be of substantial benefit, given their very short life expectancy at the time diagnosis.

1.7 ERG commentary on end of life criteria

The ERG notes that the life expectancy of patients with metastatic pancreatic cancer is short and that that the anticipated licenced population will be small. The ERG also concurs that the gain in OS for nal-iri+5-FU/LV compared with 5-FU/LV is less than 3 months (both mean and median). However, a more appropriate comparison is nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV. There is a lack of reliable evidence for this comparison. The weight of evidence from the ERG's admittedly exploratory crude comparisons suggests that OS for patients treated with oxaliplatin+5-FU/LV reported in these trials is very similar in magnitude to OS for patients who were treated with nal-iri+5-FU/LV in the NAPOLI-1 trial.

1.8 ERG commentary on the robustness of evidence submitted by the company

1.8.1 Strengths

Clinical evidence

- The company appears to have identified all relevant RCTs that assess the effectiveness of nal-iri+5-FU/LV, and relevant comparators, for the treatment of patients with metastatic pancreatic cancer who have progressed following treatment with gemcitabine
- The key trial of nal-iri+5-FU/LV (the NAPOLI-1 trial) is a phase III multi-centre, multinational, RCT of reasonable quality. The relatively large number of patients in the NAPOLI-1 trial, and the consistency of the results in a diverse population at multiple medical centres worldwide, supports the robustness of the results. Patients from the UK were recruited to the trial.

Cost effectiveness evidence

- The economic model was well constructed and easy to navigate
- The ERG's requests for further data, made via the clarification letter, were fulfilled promptly and to a good standard
- The company made an attempt to compare the cost effectiveness of nal-iri+5-FU/LV with standard NHS care (oxaliplatin+5-FU/LV) despite the absence of head-to-head effectiveness data.

1.8.2 Weaknesses and areas of uncertainty

Clinical evidence

- There is no published RCT that compares the effectiveness of nal-iri+5-FU/LV with oxaliplatin+5-FU/LV, capecitabine monotherapy or oxaliplatin+capecitabine

- Direct evidence for the clinical effectiveness of treatment with nal-iri+5-FU/LV is only available compared with 5-FU/LV, which, in clinical practice in England, is rarely given to patients who have previously received treatment with gemcitabine
- In the NAPOLI-1 trial a greater proportion of patients had received prior gemcitabine combination therapy and fewer patients had received gemcitabine monotherapy than would be seen in the NHS in England
- It is not possible to derive a credible estimate of the relative clinical or cost effectiveness of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV (which is the most commonly used regimen in this setting in NHS clinical practice). The findings from the company's ITC cannot be considered to be reliable as PH assumptions are violated and possible heterogeneity exists. The heterogeneity is both reported (in terms of trial location, patient characteristics, prior treatment with gemcitabine monotherapy versus combination therapy) and possibly unreported across the included trials
- Crude comparisons across trials conducted by the ERG suggested the PFS and OS outcomes for patients treated with oxaliplatin+5-FU/LV reported in these trials are similar in magnitude to the PFS and OS outcomes of patients who were treated with nal-iri+5-FU/LV in the NAPOLI-1 trial. The comparisons are very uncertain and may lack reliability because of potential differences in trial populations

Cost effectiveness evidence

- The use of log-normal models instead of virtually complete NAPOLI-1 trial data only served to add uncertainty to the company's cost effectiveness results
- A number of errors were made when costing treatments and adverse events
- The ERG identified an error in the utility value for the post-progression health state in the company model
- The utility values used in the company model were more reflective of the experience of patients receiving first-line, rather than second-line, treatment for pancreatic cancer
- The company's cost effectiveness results for the comparison of nal-iri+5-FU/LV with oxaliplatin+5-FU/LV must be treated with caution due to lack of effectiveness evidence and the flawed methodology used to model assumed effectiveness.

1.9 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has identified seven areas of concern relating to the approach used by the company to compare the cost effectiveness of nal-iri+5-FU/LV with 5-FU/LV. The result of implementing the ERG's preferred approach to modelling in these areas is a revised ICER of £[redacted] per QALY gained.

The ERG considers that the results (HRs) from the ITC used by the company to facilitate a comparison of the cost effectiveness of treatment with nal-iri+5-FU/LV versus oxaliplatin+5FU/LV are unreliable. The ERG cautions that the ICERs per QALY gained for this comparison are also unreliable and should not be used to inform decision-making.

2 BACKGROUND

2.1 Summary and critique of the company's description of the underlying health problem

The company's description of the underlying health problem is presented in Sections 1.3, 3.1, 3.2 and 3.4 of the company submission (CS).[1] Key points from these sections of the CS are reproduced (as bulleted items) in Box 1.

Box 1 Summary of company's description of underlying health problem

Symptoms

- Patients with pancreatic cancer are usually asymptomatic in the early stages of the disease, which, along with the deep anatomical position of the pancreas, makes the cancer difficult to detect
- Symptoms experienced in the later stages of pancreatic cancer include jaundice, abdominal pain, weight loss, poor appetite, diarrhoea, nausea and vomiting, dyspepsia, back pain, fever, blood clots, fatigue, and new onset diabetes mellitus

Incidence and survival

- Pancreatic cancer is the tenth most common cancer in the UK, and accounts for 3% of all new cases of cancer
- The incidence of pancreatic cancer in the UK was 14.7 per 100,000 people in 2013, equating to 9,408 new cases; 8,389 new cases were recorded in England and Wales (England, n=7,887 and Wales, n=(502)
- Pancreatic cancer is usually at a late stage at the time of diagnosis … 80% to 90% of patients have inoperable or metastatic disease when diagnosed
- The incidence of pancreatic cancer increases with age; it is rare in people younger than 45 years of age and 80% of cases occur in people aged between 60 and 80 years
- The mean age of onset is 71 years for men and 75 years for women
- Pancreatic cancer was responsible for 8,662 deaths in the UK in 2012, almost half of which were in people aged ≥75 years
- Only 21% of patients diagnosed with pancreatic cancer in England and Wales survive for 1 year or more after diagnosis, 3% survive for 5 years or more, and only 1% survive for 10 years or more
- The authors of a systematic review of real-world, peer reviewed, observational European studies (n=91) found that the median life expectancy at diagnosis was 4.6 months in patients with pancreatic cancer irrespective of stage of diagnosis, compared with 15.1 years for an age-matched healthy population, and the median survival for patients with metastatic disease was 2.8 to 5.7 months

Effects of disease on patients, carers and society

- Pancreatic cancer is a condition associated with particularly high burden of illness, since the vast majority of patients present with advanced disease and the symptoms experienced significantly reduce a patient's quality of life
- As well as physical symptoms in later stages of disease, depression and anxiety are also common
- The symptoms that most significantly affect a patient's quality of life compared with the general population are pain, appetite loss, and insomnia, and global health is low, as measured by the European Organisation for Research and Treatment of Cancer (EORTC-QLQ-C30) questionnaire
- The direct medical costs associated with pancreatic cancer are substantial
- The healthcare resource utilisation for patients with pancreatic cancer is high from the time of diagnosis until death

Source: CS, Sections 1.3, 3.1, 3.2 and 3.4

The Evidence Review Group (ERG) considers that the company's description largely presents an accurate picture of the underlying health problem. However, the company's statement that 80% of cases of pancreatic cancer occur in people aged between 60 and 80 years[2] is not supported by recent data. The figure of 80% is reported in guidelines published by the Pancreatic Section of the British Society of Gastroenterology in 2005 and is derived from information published in 1977[3] and 1984.[4] More recent Cancer Research UK data suggest that, between 2011 and 2013, the proportion of new cases in this age range in the UK was 55% and that 31% of new cases occur in people aged 80 years and over.[5] In the pivotal phase III NAPOLI-1 trial[6] of nal-iri+5-FU/LV described in the CS, the ERG notes that in the intention-to-treat (ITT) population, the median age was [redacted] years and the interquartile range was [redacted] years, indicating 50% of patients were aged [redacted] whereas 34% were aged 55 to 70 in the UK, 2011 to 2013.[5] Furthermore, the mean age was 63.2 and 61.0 years in the intervention and control arms of the NAPOLI-1 trial respectively, while as noted by the company in Box 1, the mean age of onset of pancreatic cancer is 71 years for men and 75 years for women.[7]

2.2 Summary and critique of the company's overview of current service provision

In addition to the summary of the company's description of the underlying health problem (see Box 1), a key message conveyed by the company is that, in contrast to many other cancers, the outlook for patients with pancreatic cancer has not improved since the 1970s. The company considers (on page 16 and on page 30 of the CS) that "there is a substantial unmet need for a new treatment that can provide extended survival in a patient population that is currently underserved." The company makes the point that pancreatic cancer grows within a dense, poorly perfused, and nearly impenetrable stroma that limits the ability of current chemotherapies to effectively reach the tumour and achieve effective concentrations.[8] The company highlights that the authors of two All-Party Parliamentary Group (APPG) reports (one published in 2013[9] and the other in 2014[10]) called for more and better treatments for patients with pancreatic cancer and recommended that patients should receive prompt and up-to-date treatment.

The company's overview of current service provision is presented in Sections 1.3, 3.3, 3.5, 3.6 and 3.7 of the CS. Key points from these sections are reproduced (as bulleted items) in Box 2. Overall, the ERG agrees with the company's overview of current service provision but makes three additional points in relation to first-, second- and third- line treatments (see Sections 2.2.1, 2.2.2 and 0 of the ERG report).

Box 2 Summary of company's overview of current service provision

Treatment for patients with early stage disease

- Surgery is the only potentially curative option for pancreatic cancer, but it is only possible for the 10% to 20% of people who present with early stage disease
- Of these patients, 53% to 87.5% have recurrence of their disease despite surgical removal of the tumour

First-line treatment for pancreatic cancer

- Patients with locally advanced or metastatic disease are not suitable for surgical resection, and at the time of diagnosis, 35% to 40% of people have locally advanced disease and 45% to 55% have metastases
- In the UK, gemcitabine is the most commonly prescribed first-line chemotherapy for pancreatic cancer; 46% of patients are administered gemcitabine as first-line therapy, and a further 34% are given gemcitabine in combination with another cytotoxic agent
- Gemcitabine is also the only treatment option that is recommended by NICE as first-line therapy in patients who are not suitable for potentially curative surgery and who have a Karnofsky performance score of ≥50
- The British Society of Gastroenterology (BSG) published guidelines for the management of patients with pancreatic cancer in 2005, following the approval of gemcitabine by NICE in 2001
- The BSG guidelines recommend that gemcitabine should be used as chemotherapy for palliation, and that therapy with novel treatments should only be offered to patients within clinical trials
- There is a poor response rate (20% or less) to gemcitabine-based treatment in the first-line setting and a short progression-free survival (PFS= <4 months)
- An increased use of gemcitabine as adjuvant treatment means that a different treatment may be required on progression

Second-line treatment for advanced and metastatic disease

- Patients who progress on gemcitabine form a substantial patient pool, yet are currently poorly served, with no licensed or NICE recommended treatments available
- Clinical expert opinion has revealed that in the UK, 20% to 40% of patients treated with gemcitabine are well enough to receive active treatment post-gemcitabine
- There is currently no licensed or approved therapies in this setting
- There is currently no standard of care for treatment following disease progression on gemcitabine-based therapy
- Unlicensed treatments are currently used, and their use is supported by lower and conflicting levels of evidence than is considered acceptable in many other cancer indications
- The majority of patients receive one of the FOLFOX regimens containing folinic acid (leucovorin, LV), 5-FU 5-fluorouracil and oxaliplatin. The most commonly used FOLFOX regimen in England is modified FOLFOX4 (mFOLFOX4)
- Very few patients…receive oxaliplatin in combination with capecitabine or receive fluoropyrimidine monotherapy as post-gemcitabine treatment
- It is important to recognise that peripheral neuropathy is a frequent treatment-related adverse event (AE) for oxaliplatin-containing chemotherapy regimens, and is often a cause for dose reductions within the chemotherapy treatment
- Given the conflicting results of these unlicensed treatments and the evidence supporting overall survival improvements with pegylated liposomal irinotecan hydrochloride trihydrate, (nal-iri), it is expected that nal-iri will provide the best option for the treatment of gemcitabine-refractory patients
- The European Society for Medical Oncology (ESMO) guidelines state that nal-iri may be the best option for the treatment of gemcitabine-refractory patients

Source: CS, Sections 1.3, 3,3, 3.5, 3.6 and 3.7

2.2.1 First-line treatment for metastatic pancreatic cancer

The company states that the majority of patients are treated with gemcitabine at first-line. Those who are not treated with gemcitabine are mostly treated with oxaliplatin in combination with 5-fluorouracil (5-FU), leucovorin (LV) and irinotecan, also known as FOLFIRINOX (FOL=Folinic acic [LV], F=5-FU, IRIN=irinotecan, OX=oxaliplatin.)

In the study (Smyth 2015[11]) cited by the company, 80% of 191 UK patients with metastatic pancreatic cancer who were diagnosed between 1 January 2009 and 31 December 2012 were treated with gemcitabine (46% monotherapy, 34% combination therapy), 12% were treated with FOLFIRINOX and other treatments accounted for the remaining 8% of the population. The ERG notes that the data from the Smyth study are derived from a purposive sample (of 50 physicians in the UK and 53 physicians in France) rather than a random sample. The ERG is aware that the first randomised controlled trial (RCT) to show evidence of the effectiveness of FOLFIRINOX versus gemcitabine as a first-line treatment was not published until 2011,[12] and so prior to this, and at the time of the Smyth 2015 study,[11] FOLFIRINOX was less commonly used than it is now. Clinical advice to the ERG is that FOLFIRINOX is used in the NHS in England in approximately 15% to 20% of cases (being an option only for fitter patients, most likely those with ECOG PS 0 to 1). Indeed, the ERG notes that in the 2014 STA for nab-paclitaxel in combination with gemcitabine for the treatment of metastatic pancreatic cancer,[13] it was reported by the manufacturer that, in clinical practice in England and Wales, 49% of patients received gemcitabine monotherapy, 25% received combination therapy (gemcitabine in combination with capecitabine) and 19% received FOLFIRINOX. Nab-paclitaxel in combination with gemcitabine was not recommended by NICE. Expert advice received by the ERG is that in some geographical areas of England, the proportion of patients treated with FOLFIRINOX in the NHS may be higher than 20%.

2.2.2 Second-line treatment for metastatic pancreatic cancer

The company argues that:

> "Patients who progress on gemcitabine form a substantial patient pool, yet are currently poorly served, with no licensed or NICE recommended treatments available. Therefore, unlicensed treatments are currently used, and their use is supported by lower and conflicting levels of evidence than is considered acceptable in many other cancer indications." (CS, page 16)

The company notes that in England, oxaliplatin in combination with 5-FU/LV (oxaliplatin+5-FU/LV) is the most commonly used treatment for this patient population. Oxaliplatin+5-FU/LV regimens are commonly known as FOLFOX (FOL=Folinic acid [LV], F=5-FU, OX=oxaliplatin). Modified versions of FOLFOX regimens exist, e.g. modified FOLFOX4 (mFOLFOX4), modified FOLFOX6 (mFOLFOX6) and a regimen known as OFF (oxaliplatin, folinic acid [LV], fluorouracil [5-FU]). These regimens differ in terms of the cumulative dose of 5-FU, the use of bolus 5-FU, the total dose of oxaliplatin, and the overall scheduling of treatment. A comparison of the different regimens is presented in Table 1. The ERG is not aware of any RCT evidence to suggest that any particular regimen is more effective than any other in terms of efficacy or safety.

Table 1 Typical oxaliplatin+5-FU/LV regimens described in the literature and used in clinical practice

Regimen details	UK clinical practice		Clinical trials (unpublished)		Published trial
	mFOLFOX4	mFOLFOX6	mFOLFOX6 (PANCREOX)	mFOLFOX6 (SWOG S1115)	OFF (CONKO-003)
Oxaliplatin dose	85 mg/m^2 Day 1	85 mg/m^2 Day 1	85 mg/m^2 Day 1	85 mg/m^2 Day 1	85 mg/m^2 Days 8 and 22
Oxaliplatin infusion time	2 hours	2 hours	2 hours	2 hours	Not specified
5-FU bolus dose	400 mg/m^2 Day 1	400 mg/m^2 Day 1	400 mg/m^2 Day 1	--	--
5-FU bolus time	2 hours	2 hours	2 hours (with oxaliplatin)	--	--
5-FU infusion dose	1600 mg/m^2 Day 1	2400 mg/m^2 Day 1	2400 mg/m^2 Day 1 to 2	2400 mg/m^2 Day 1 to 2	2000 mg/m^2 Days 1, 8, 15 and 22
5-FU infusion time	46 hours	46 hours	46 hours	46 to 48 hours	24 hours
Leucovorin dose	200 mg/m^2 Day 1	350 mg/m^2 Day 1	400 mg/m^2 Day 1	--	200 mg/m^2 Days 1, 8, 15 and 22
Leucovorin infusion time	2 hours	2 hours	2 hours (with oxaliplatin)	--	Not specified
Cycle length	14 days	14 days	14 days	14 days	42 days
Cumulative 6-week dose					
Oxaliplatin	255 mg/m^2	255 mg/m^2	255 mg/m^2	255 mg/m^2	170 mg/m^2
5-FU	6000 mg/m^2	8400 mg/m^2	8400 mg/m^2	7200 mg/m^2	8000 mg/m^2
Leucovorin	600 mg/m^2	1050 mg/m^2	1200 mg/m^2	--	800 mg/m^2

-- Not applicable (i.e. no use of bolus 5-FU and/or no explicit mention is made that 5-FU was modulated with leucovorin)
Source: Company response to ERG clarification letter, adapted from Table 2

Clinical advice to the ERG is that the OFF regimen is rarely used in England, if at all. Within the CS there is a lack of clarity as to which is the most commonly used FOLFOX regimen in the NHS:

- mFOLFOX4 is stated to be the most commonly used FOLFOX regimen in England (CS, page 16)

- FOLFOX6 is stated to be the most commonly used FOLFOX regimen in the UK (CS, page 130)
- Key opinion leaders (KOLS) estimate that 40% of post-gemcitabine metastatic pancreatic cancer patients who are eligible for further treatment would receive either mFOLFOX4 or FOLFOX6 (CS, page 98)

In response to the ERGs clarification request, the company presented findings from the opinions of six KOLS based in the UK who were consulted regarding the treatment they used in clinical practice for patients with disease progression on gemcitabine (Table 2). The findings clearly show that practice varies within the UK but that, essentially, the most common regimen is either mFOLFOX4 or mFOLFOX6, depending on geographical area. Clinical advice to the ERG (Table 2) is that mFOLFOX6 is the most common treatment regimen.

Table 2 Most commonly used post-gemcitabine treatments cited by clinical experts

Clinician	Treatment used following gemcitabine (for patients who are well enough for further treatment)	Oxaliplatin+5-FU/LV regimen used
1	80% oxaliplatin+5-FU/LV 20% oxaliplatin+capecitabine	mFOLFOX4
2	Only oxaliplatin+5-FU/LV	mFOLFOX4
3	80% to 90% oxaliplatin+5-FU/LV 20% oxaliplatin+capecitabine	mFOLFOX6
4	Only oxaliplatin+5-FU/LV	mFOLFOX4
5	Mainly oxaliplatin+5-FU/LV Sometimes capecitabine monotherapy	mFOLFOX4
6	Mainly oxaliplatin+5-FU/LV Rarely fluoropyrimidine monotherapy – less than 10% Extremely rare use of oxaliplatin+capecitabine	mFOLFOX6
ERG*	75% oxaliplatin+5-FU/LV 25% capecitabine monotherapy	mFOLFOX6

Source: Company response to ERG clarification letter' Table 1 and *clinical advice received by the ERG

The findings in Table 2 also show that the extent of treatment other than oxaliplatin+5-FU/LV also varies by geographical area. As the company has stated: "Very few patients, if any, receive oxaliplatin in combination with capecitabine [oxaliplatin+capecitabine] … as post-gemcitabine treatment" (CS, page 16). However, the company also states in the CS that very few patients receive fluoropyrimidine monotherapy as post-gemcitabine treatment. Fluoropyrimidine monotherapy tends to be preferred where patients are not considered able to tolerate oxaliplatin and may comprise capecitabine monotherapy or 5-FU/LV. Capecitabine monotherapy tends to be the fluoropyrimidine monotherapy used by most clinicians in such situations. Indeed, the ERG notes that in the Smyth 2015[11] study, the most commonly used second-line treatments (not necessarily post-gemcitabine) for patients with metastatic pancreatic cancer were capecitabine monotherapy (27.6%),

oxaliplatin+capecitabine (24.1%) and gemcitabine (10.3%). Clinical advice received by the ERG is that gemcitabine is most commonly used for patients previously treated with FOLFIRINOX. It is not commonly used for patients who have previously been treated with gemcitabine but may be used again in some instances where patients have been disease-free after completing treatment with gemcitabine for a relatively long time (e.g. 12 months).

2.2.3 Third-line treatment for metastatic pancreatic cancer

The ERG notes that very few patients with metastatic pancreatic cancer live long enough to receive third-line treatment. In the aforementioned Smyth 2015[11] study only 1 (0.5%) out of 191 patients in the UK sample received a third-line treatment. The specific regimen received by the patient is not known.

2.2.4 Pegylated liposomal irinotecan hydrochloride trihydrate

Pegylated liposomal irinotecan hydrochloride trihydrate (nal-iri) does not currently have a marketing authorisation from the Committee for Human Medicinal Products (CHMP). CHMP positive opinion is expected circa 21 July 2016. If approved, it is anticipated that it will be provided in combination with 5-fluorouracil (5-FU) and folinic acid (also known as leucovorin [LV]) for the treatment of metastatic adenocarcinoma of the pancreas, in adult patients who have progressed following gemcitabine-based therapy, i.e. after previous treatment with gemcitabine in any setting: adjuvant, neoadjuvant, first-line metastatic, second-line metastatic or even later.

Nal-iri is a nanoliposomal formulation of the anti-cancer drug irinotecan. Irinotecan is a derivative of camptothecin, which inhibits the DNA enzyme topoisomerase I. It is converted by non-specific carboxylesterases present in the liver, blood and macrophages[14] into its metabolite SN-38, which is 100- to 1000-fold more active than irinotecan. Whilst non-liposomal irinotecan is sometimes used as a component drug of the FOLFIRINOX regimen (i.e. in combination with oxaliplatin+5-FU/LV) as a first-line treatment for metastatic pancreatic cancer, it is rarely used as a second-line or later treatment. It has, however, been studied in combination with 5-FU/LV (but not with oxaliplatin) as part of a regimen known as FOLFIRI (folinic acid [LV], 5-FU, irinotecan).[12,15-17]

The rationale for developing a nanoliposomal formulation of irinotecan is that nanoliposomes are expected to accumulate within the tumour and release irinotecan slowly over time. This should yield a higher concentration of chemotherapeutic agent in the tumour, decrease the rate at which it is removed from the body and result in better tumour shrinkage or slower

tumour growth than could be obtained with non-liposomal irinotecan. The ERG is not, however, aware of any clinical trial that has compared nal-iri with non-liposomal irinotecan.

As highlighted in Box 2, the company expects that nal-iri in combination with 5-FU/LV (nal-iri+5-FU/LV) will provide the best option for the treatment of gemcitabine-refractory patients, a statement supported in the European Society for Medical Oncology (ESMO) guidelines. However, based on clinical opinion received, the ERG considers nal-iri+5-FU/LV is likely to be preferred for patients who are considered to be at risk of peripheral neuropathy, which is a frequent treatment-related adverse event (AE) for patients treated with regimens containing oxaliplatin. The company also expects that, if recommended by NICE, take-up of nal-iri+5-FU/LV will be gradual. It estimates that only 5% of patients potentially eligible for treatment post-gemcitabine would actually receive nal-iri+5-FU/LV in the first year it becomes a treatment option.

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

Table 3 summarises the decision problem described by the company in the CS in relation to the final scope issued by NICE. Each parameter is discussed in more detail (Section 3.1 to Section 3.7) in the text following Table 3.

Table 3 Final scope issued by NICE and company's decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission
Population	People with metastatic adenocarcinoma of the pancreas that has been treated with gemcitabine-based treatments	Adult patients who have progressed following gemcitabine-based therapy (reflecting trial evidence and the anticipated therapeutic indication in the draft Summary of Product Characteristics; nal-iri does not currently have a marketing authorisation)
Intervention	Pegylated liposomal irinotecan hydrochloride trihydrate in combination with fluorouracil and folinic acid	As per scope
Comparator (s)	• Oxaliplatin in combination with fluorouracil and folinic acid [leucovorin] • Oxaliplatin in combination with capecitabine • Fluoropyrimidine monotherapy	• Oxaliplatin in combination with fluorouracil and folinic acid (oxaliplatin+5-FU/LV) • 5-fluorouracil+leucovorin (5-FU/LV) (a fluoropyrimidine monotherapy) Oxaliplatin in combination with capecitabine is not included a comparator due to a lack of evidence to enable a comparison; this regimen is not commonly used in clinical practice in England
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • Health related quality of life	As per scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality adjusted life year The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective	As per scope
Subgroups to be considered	None specified	As per scope
Other considerations	Guidance will only be issued in accordance with the marketing authorisation Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	A Patient Access Scheme (PAS) is currently being considered by the PAS Liaison Unit The company highlights appropriate access to a treatment such as nal-iri+5-FU/LV should improve the patient experience for patients with rarer forms of cancer, such as metastatic pancreatic cancer and therefore for elderly patients (i.e. improve equity)

Source: Final scope issued by NICE and CS, Table 1

3.1 Population

The company has provided evidence for the population for which it expects the intervention to be licensed (since nal-iri does not currently have a marketing authorisation; CHMP positive opinion is expected circa 21 July 2016), i.e. treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil (5-FU) in adult patients who have progressed following gemcitabine-based therapy. The company highlights that patients who have progressed following gemcitabine-based therapy can include patients previously treated with monotherapy or combination therapy. The ERG notes that the licence, if granted, will be largely based on the clinical results from the NAPOLI-1 trial. In the NAPOLI-1 trial, patients were allowed to have received previous gemcitabine therapy in any setting, i.e. in the adjuvant or neoadjuvant setting (12.2%) first-line (56.1%) or second- line or later (31.7%) treatment for metastatic pancreatic cancer.

3.2 Intervention

The intervention is pegylated liposomal irinotecan hydrochloride trihydrate (nal-iri) in combination with 5-FU and folinic acid (also known as leucovorin [LV]). As noted above, the intervention is not currently licensed.

The recommended dose and regimen of nal-iri is 80 mg/m^2 administered intravenously over 90 minutes, diluted prior to administration with 5% glucose solution or 0.9% sodium chloride solution for injection to a final volume of 500 mL; it must not be administered as a bolus injection or an undiluted solution. Nal-iri is then followed by LV 400 mg/m^2 administered intravenously over 30 minutes, followed by 5-FU 2400 mg/m^2 administered intravenously over 46 hours. Nal-iri+5-FU/LV is administered every 2 weeks.

A reduced starting dose of nal-iri of 60 mg/m^2 should be considered for patients known to be homozygous for the *UGT1A1*28* allele (since patients homozygous for this allele have been found to be at increased risk of developing haematological (e.g. neutropenia) and/or digestive toxicities).[18] A dose increase of nal-iri to 80 mg/m^2 should be considered if tolerated in subsequent cycles. The ERG notes that testing for *UGT1A1*28* is not routinely conducted in NHS clinical practice. Therefore, if nal-iri+5-FU/LV was to be used in clinical practice without prior testing, this may mean that some AEs reported in the NAPOLI-1 trial would occur more often in clinical practice, resulting in more dose reductions which would likely be required as a result. The ERG also notes that in healthy individuals, it has been estimated that the proportion of people homozygous for *UGT1A1*28* is higher in people with varying degrees of African ancestry (18.1%) than Caucasians of European ancestry (11.3%) or Asians of Chinese and Japanese descent (2.1%).[19]

As described in Section 2.2 of this ERG report, 5-FU/LV is also used as a first-line treatment as part of the FOLFIRINOX regimen and as a second-line treatment as part of the FOLFOX regimen. The cumulative dose of 5-FU/LV, and whether bolus 5-FU is used, varies in the FOLFOX regimens (see Section 2.2, Table 1). The dose and scheduling for 5-FU/LV in combination with nal-iri is similar to the dose and scheduling for 5-FU/LV in combination with oxaliplatin in the mFOLFOX6 regimen. The only difference is that the mFOLFOX6 regimen used in England typically includes a bolus injection of 5-FU prior to it being infused over 46 hours, whereas in combination with nal-iri, there is no bolus injection of 5-FU prior to it being infused over 46 hours.

3.3 Comparators

The final scope issued by NICE and the company's decision problem identify three comparators:

- oxaliplatin+5-FU/LV
- oxaliplatin+capecitabine
- fluoropyrimidine monotherapy.

The company only compares the clinical effectiveness of nal-iri+5-FU/LV with 5-FU/LV (a fluoropyrimidine monotherapy). Both 5-FU/LV and oxaliplatin+5-FU/LV are comparators to nal-iri+5-FU/LV in the company's economic evaluation.

As highlighted in Section 2.2, oxaliplatin+5-FU/LV is the most commonly used second-line treatment for patients with metastatic pancreatic cancer in England and different formulations of oxaliplatin+5-FU/LV exist; mFOLFOX4 and FOLFOX6 are the most commonly used formulations in England, depending on geographical area. Nal-iri+5-FU/LV has not been compared with any oxaliplatin+5-FU/LV regimen in clinical trials. To allow a comparison of cost effectiveness to be undertaken, the company has conducted an indirect treatment comparison (ITC) to generate clinical effectiveness results for treatment with nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV. In its approach, the company assumes the OFF and mFOLFOX6 regimens administered in the CONKO-003 and PANCREOX trials are representative of the efficacy of oxaliplatin+5-FU/LV. As oxaliplatin+5-FU/LV is the most commonly used regimen in England, the ERG acknowledges that the company's attempt to make this comparison was appropriate and that, in the absence of evidence to the contrary, all oxaliplatin+5-FU/LV regimens may be considered to be of equal efficacy in clinical practice (see also Section 4.7 of this ERG report). However, for reasons outlined in Section 4.3 of this ERG report, the ERG agrees with the company that the results from the ITC cannot be considered reliable.

Clinical advice to the ERG and clinical advice received by the company suggests 5-FU/LV monotherapy is only rarely used as a second-line treatment for metastatic pancreatic cancer in England (see Section 2.2.2 of this ERG report). 5-FU/LV was, however, the comparator to nal-iri+5-FU/LV in the NAPOLI-1 trial. The rationale for choosing 5-FU/LV as the comparator in the NAPOLI-1 trial was that 5-FU was historically one of the mainstays of therapy for pancreatic cancer until the approval of gemcitabine. Moreover, it had been used as a comparator to the OFF regimen in the recently completed CONKO-003 trial, and the demonstrated responses in the 5-FU/LV control arm were argued by the company to suggest that it was effective and, therefore, the optimal choice when the NAPOLI-1 trial was planned. The ERG notes that at the time the NAPOLI-1 trial was designed, the results from the CONKO-003 trial comparing OFF with 5-FU/LV had not actually been published but results comparing OFF with BSC and OFF with 5-FU/LV had been presented at the conference of the American Society of Clinical Oncology (ASCO) in 2005[20] and 2008[21] respectively. These were suggestive of a survival benefit for OFF and so it could be argued that OFF may have been a more appropriate comparator.

The ERG notes that, when gemcitabine was recommended as a first-line regimen by NICE in 2001,[22] evidence was primarily derived from one published trial (Burris 1997[23]) comparing gemcitabine with 5-FU. The dose and scheduling of 5-FU/LV used in the CONKO-003 trial, and adopted for use as a comparator in the NAPOLI-1 trial, differed markedly to the regimen in the Burris trial. However, the regimen in the CONKO-003 and NAPOLI-1 trials is more typical of that used in NHS clinical practice (Table 4).

In the NAPOLI-1 trial, the scheduling of 5-FU/LV in the control arm of the NAPOLI-1 trial differed to that in the intervention arm (in combination with nal-iri) (Table 4). The company argues that the difference in scheduling is highly unlikely to have created a bias in favour of the nal-iri+5-FU/LV arm, since the planned and recorded dose intensities of 5-FU were higher in the control arm.

Table 4 5-FU/LV regimens used in trials versus gemcitabine, and in combination with and versus oxaliplatin and nal-iri

Regimen details	Burris 1997	CONKO-003		NAPOLI-1	
	Versus gemcitabine	Versus oxaliplatin+5-FU/LV	With oxaliplatin+5-FU/LV	Versus nal-iri+5-FU/LV	With nal-iri+5-FU/LV
5-FU bolus dose	600 mg/m^2 Days 1, 8, 15, 22	--	--	--	--
5-FU bolus time	30 mins	--	--	--	--
5-FU infusion dose	--	2,000 mg/m^2 Days 1, 8, 15 and 22	2,000 mg/m^2 Days 1, 8, 15 and 22	2,000 mg/m^2 Days 1, 8, 15 and 22	2,400 mg/m^2 Day 1 to 2
5-FU infusion time	--	24 hours	24 hours	24 hours	48 hours
Leucovorin dose	--	200 mg/m^2 Days 1, 8, 15 and 22	200 mg/m^2 Days 1, 8, 15 and 22	200 mg/m^2 Days 1, 8, 15 and 22	400 mg/m^2 Day 1
Leucovorin infusion time	--	Not specified	Not specified	Not specified	Not specified
Cycle length	4 weeks	2 weeks	2 weeks	6 weeks	2 weeks
Cumulative 6-week dose					
5-FU	3,600 mg/m^2	8,000 mg/m^2	8,000 mg/m^2	8,000 mg/m^2	7,200 mg/m^2
Leucovorin	--	1,200 mg/m^2	1,200 mg/m^2	1,200 mg/m^2	800 mg/m^2

-- Not applicable
Note: Bolus 5-FU was not used in any of the three trials.

The company states that it was unable to derive comparative evidence for nal-iri+5-FU/LV versus oxaliplatin+capecitabine or capecitabine monotherapy. As highlighted in Section 2.2.2, whilst the ERG understands that neither capecitabine nor oxaliplatin+capecitabine are commonly used in England in this patient population, both regimens are more commonly used than 5-FU/LV.

A third fluoropyrimidine therapy that could, theoretically, have been considered by the company is S-1 which, like capecitabine, is an oral treatment. The company stated that it excluded S-1 from consideration (CS, Table 6) because it is only used in combination with other treatments. Clinical advice to the ERG is that S-1 can also be used as a monotherapy. However, it is rarely used in England, if at all, and so the ERG considers it was appropriate for the company not to have included this potential comparator.

3.4 Outcomes

The outcomes specified in the final scope issued by NICE are overall survival (OS), progression-free survival (PFS), response rates, AEs and health related quality of life (HRQoL); these are standard outcomes used in oncology clinical trials. Clinical evidence is reported in the CS for all outcomes specified in the final scope issued by NICE.

3.5 Economic analysis

As specified in the final scope issued by NICE, the cost effectiveness of treatments is expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes are assessed over a 10-year time horizon (equivalent to a lifetime horizon) and costs are considered from an NHS perspective. Effectiveness evidence from the NAPOLI-1 trial was used in the company model to generate results for the comparison of the cost effectiveness of nal-iri+5-FU/LV versus 5-FU/LV. Outputs from the company's ITC (which both the company and the ERG consider to be unreliable) were used to generate cost effectiveness results for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV.

3.6 Subgroups

No subgroups were specified in the final scope issued by NICE. The company also states that no subgroup analyses were considered in its decision problem. The ERG concurs with the company that there were no relevant subgroups.

3.7 Other considerations

The company has submitted a Patient Access Scheme (PAS) application. This is currently undergoing consideration by the PAS Liaison Unit. The cost effectiveness results presented in the CS have not been generated using the proposed PAS price.

Regarding equity, the company highlights that pancreatic cancer is also an orphan disease[24] (i.e. a disease that is considered to be relatively rare, defined as no more than 5 people in 10,000). The company reports findings from the 2014 National Cancer Patient Experience Survey[25] in which people with rarer forms of cancer (including 4310 patients with upper gastrointestinal cancer) tended to report a poorer experience of their treatment and care than people with more common forms of cancer. In addition, the company notes that pancreatic cancer presents primarily in the elderly population[2] and equity of treatment of the elderly is a concern, citing a report published by the National Audit Office in January 2015. For example, in the report it is stated that across all cancers, patients aged 55 to 64 years are 20% more likely to survive for at least 1 year after diagnosis than those aged 75 to 99 years. Therefore, the company argues that the provision of nal-iri+5-FU/LV as a treatment for patients with pancreatic cancer will address some of these equity issues. However, the ERG notes that while pancreatic cancer does present more often in older patients, with a mean onset of 71 years for men and 75 years for women, evidence for the clinical effectiveness of nal-iri+5-FU/LV in the NAPOLI-1 trial is derived from a patient population with a median age of [redacted] years. The ERG further cautions, based on clinical advice received,

that clinicians would be wary of using combination chemotherapy in many older adults aged over 75 years of age since they tend to be frailer and therefore less likely to cope with this type of treatment.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Systematic review methods

A summary of the systematic review methods employed by the company, along with ERG comments, is presented in Table 5. Overall, the ERG is satisfied that the company's review was comprehensive and that the eligibility criteria employed were consistent with the final scope issued by NICE and with the company's decision problem.

Table 5 Summary of, and ERG comments on, the company's systematic review methods

Review method	ERG comment
Searching	
• The systematic review was designed to identify studies investigating nal-iri+5-FU/LV and/or comparators that may be relevant to the NICE decision problem and that of other HTA bodies • One search was carried out to identify RCTs, non-randomised studies and observational studies on 21 January 2016 Databases searched (along with date limits) were: MEDLINE® In-Process & Other Non-Indexed Citations, and MEDLINE®: 1946 to present; Embase: 1980 to 2016 and the Cochrane Library, incorporating: Cochrane Central Register of Controlled Trials (CENTRAL) – December 2015; Cochrane Database of Systematic Reviews – 2005 to 13 January 2016; Database of Abstracts of Reviews of Effects (DARE) – 2nd Quarter 2015; Health Technology Assessment (HTA) – 4th Quarter • Grey literature sources were also searched: ASCO, ESMO, ISPOR, Clinicaltrials.gov, NCI trials database, ISRCTN registry, UKCCR, EORTC and UK clinical trials gateway	• Where available, appropriate search terms were used; however, the search strategy reported by the company in its appendices to the CS includes a search filter for RCTs • Company included RCT filter for the Cochrane library which is not relevant for the Cochrane library search database • The company searched the appropriate conference abstracts • The ERG was able to replicate the searches • The ERG verified the data in the PRISMA flowchart presented in the CS via the clarification process • The ERG is confident that no relevant studies were missed
Eligibility criteria	
• Studies identified by the electronic searches were independently assessed by two reviewers to ascertain whether they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by a third party	• Use of two independent assessors improves quality of review • A two-stage method for including studies as employed by the company (initially identifying references from title/abstracts and then full text) is considered to be good practice
Data extraction	
• A reviewer extracted relevant information into the STA template. A second reviewer checked the data extraction and any inconsistencies were resolved through discussion	• Use of two independent assessors improves quality of data extraction
Quality assessment and risk of bias	
• Descriptive critical appraisal of the only included RCT was undertaken using the method recommended by NICE[26] • Descriptive critical appraisal of two RCTs used to derive evidence for oxaliplatin+5-FU/LV in the company's cost effectiveness analysis was also undertaken using the NICE recommended method	• An appropriate method for assessing risk of bias in RCTs was used • Unclear if two independent assessors were employed for assessing risk of bias

CS=company submission; RCT=randomised controlled trial; PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ASCO= American Society of Clinical Oncology; ESMO= European Society for Medical Oncology; ISPOR= International Society For Pharmacoeconomics and Outcomes Research; NCI trials database=National Cancer Institute trials database; UKCCR= United Kingdom Coordinating Committee On Cancer Research; EORTC=European Organisation for Research and Treatment of Cancer

4.1.2 Evidence synthesis

The company's literature search led to the identification of one RCT that was considered to be directly relevant to the decision problem (the NAPOLI-1 trial). This trial compared treatment with nal-iri+5-FU/LV with 5-FU/LV; the company considered 5-FU/LV to be a relevant comparator (but, as explained in Section 3.3 of this ERG report, this decision is disputed by the ERG). With the inclusion of only one relevant study, it was not possible for the company to carry out a meta-analysis.

The methods and results from a non-randomised study (NCT00813163[27]) that was designed to assess the effectiveness of nal-iri monotherapy, was reported in the CS and was described as 'supporting evidence'. (The ERG notes that this study was excluded from the company's systematic review).

To compare the effectiveness of nal-iri+5-FU/LV with other comparators, a "best-case evidence network scenario" was constructed (reproduced in this ERG report in Section 4.3, Figure 1). This network showed that an ITC allowing the comparison of the effectiveness of nal-iri+5-FU/LV with oxaliplatin+5-FU/LV (but no other relevant comparators) might, theoretically, be possible. However, the company states that it was not feasible to conduct an ITC due to the PH assumptions being violated for both OS and PFS data and also due to heterogeneity between trials and limited reporting. This view was supported by the panel of three KOLS who were consulted by the company. No clinical efficacy results are presented in the clinical effectiveness section of the CS for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV (although, results from an ITC conducted by the company are used in the company's cost effectiveness model). The clinical effectiveness section of the CS comprises narrative descriptions and findings from the NAPOLI-1 trial and the non-randomised NCT00813163.

The ERG considers that the company's approach to evidence synthesis is appropriate. The ERG is satisfied that appropriate steps were taken to compare nal-iri+5-FU/LV with relevant comparators and agrees that there were methodological issues precluding the conduct of an ITC which could produce credible results (detailed further in Section 4.3 of this ERG report). However, the ERG considers that it would have been useful if the company had presented results tables describing the efficacy and safety of relevant comparators, in particular for oxaliplatin+5-FU/LV. Therefore, to facilitate a crude comparison of nal-iri+5-FU/LV with other relevant comparators (in particular, oxaliplatin+5-FU/LV) the ERG has extracted efficacy and safety data from the key trials identified by the company's systematic review and presented these data in Section 4.7.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 Identified studies in the systematic review

The company states that 31 records, reporting 28 different studies, were included in its systematic review (CS, Figure 3). These included 16 publications of 13 RCTs and reports for 15 non-randomised studies (CS, Table 7). As noted in Section 4.1.1 (Table 5) of this ERG report, the systematic review was designed to identify studies investigating the effectiveness of nal-iri+5-FU/LV and/or its comparators. Only one RCT (the NAPOLI-1 trial) included nal-iri+5-FU/LV as an intervention and none of the non-randomised studies investigated nal-iri+5-FU/LV. Thus, the ERG considers that the NAPOLI-1 trial is the only study directly relevant to the final scope issued by NICE and the company's decision problem. The comparator in this trial was 5-FU/LV (a fluoropyrimidine monotherapy which, as highlighted in Section 2.2.2 and Section 3.3 is rarely used in this setting in England). To compare the effectiveness of nal-iri+5-FU/LV with other (more) relevant comparators (e.g. oxaliplatin+5-FU/LV), the company explored the feasibility of conducting a network meta-analysis (NMA) or ITC (see Section 4.3 of this ERG report).

4.2.2 Characteristics of the NAPOLI-1 trial

The NAPOLI-1 trial is a phase III open-label RCT that investigated the use of nal-iri, with or without 5-FU/LV versus 5-FU/LV in patients with metastatic pancreatic cancer previously treated with a gemcitabine-based therapy. The NAPOLI-1 trial was conducted in 76 study sites across North America, Europe, Asia, South America and Oceania. There were four sites in the UK and these enrolled a total of 28 patients.

The NAPOLI-1 trial was originally designed to compare the effectiveness of nal-iri monotherapy versus 5-FU/LV, and patients were initially randomised to these two treatment arms in a 1:1 ratio. However, when safety data for the combination of nal-iri+5-FU/LV became available (from a phase II RCT of metastatic colorectal cancer known as PEPCOL[28]), this combination treatment was shown to have a favourable safety profile compared to FOLFIRI in terms of common grade 3 to 4 AEs, with no additional safety concerns identified. For this reason, the NAPOLI-1 trial protocol was amended so that a third treatment arm could be added to the study (version 2); patients in this new treatment arm received nal-iri+5-FU/LV. The company explains in the CS that only data from the nal-iri+5-FU/LV and the 5-FU/LV arms are of relevance to this appraisal and so efficacy data are presented for these two arms only; the ERG has adopted the same approach in the ERG report. The company also explains that, in order to accurately compare the efficacy of nal-

iri+5-FU/LV with 5-FU/LV, an analysis group was used that only included the patients who were randomised to 5-FU/LV under protocol version 2 or later. Therefore patients that were randomised to the control arm prior to the protocol amendment are not included in the efficacy analyses presented in the CS. The ERG considers that this approach is appropriate, as it maintains the benefit of randomisation (i.e. balancing baseline characteristics between treatment groups).

Due to a possible association between homozygosity of the *UGT1A1*28* allele and irinotecan toxicity, patients were required to undergo *UGT1A1* genotype testing prior to enrolment in the NAPOLI-1 trial. Patients who were identified as being homozygous for the *UGT1A1*28* allele, and who were randomised to either the nal-iri+5-FU/LV arm or the nal-iri monotherapy arm started treatment at a reduced dose, which was increased if no drug-related toxicity was experienced after the first administration of nal-iri. Clinical advice to the ERG is that no such testing is currently performed in clinical practice in England and so the nal-iri dose would likely be initiated at 80mg/m^2 and reduced when drug-related toxicity occurred. The company reports that in the NAPOLI-1 trial, homozygosity of the *UGT1A1*28* allele was observed in 23/243 (9.5%) Caucasians, in 2/129 (1.6%) Asians and in 2/26 (7.7%) of all other races. These results are in line with those reported elsewhere in the literature; for example, Beutler (1998)[19] reports a prevalence of homozygosity of the *UGT1A1*28* allele in 11.3% of Europeans, and in 2.1% of Asians.

Randomisation was stratified according to baseline albumin levels (≥4.0 g/dL versus <4.0 g/dL), KPS (70 and 80 versus ≥90), and ethnicity (Caucasian versus East Asian versus all others).

The primary endpoint of the NAPOLI-1 trial was OS. Secondary endpoints included PFS, time to treatment failure (TTF), objective response rate (ORR), tumour marker response, CBR, AEs and HRQoL.

4.2.3 Patient characteristics in the NAPOLI-1 trial

The company provided baseline characteristics for the patients included in the two relevant arms of the NAPOLI-1 trial (see Table 6).

As noted in Section 2.2.1, it has been reported that in clinical practice in England and Wales, 49% of patients received gemcitabine monotherapy and 25% received gemcitabine in combination with capecitabine for metastatic pancreatic cancer. This equates to two thirds of patients treated with gemcitabine receiving monotherapy and one-third receiving combination therapy. However, in the NAPOLI-1 trial, 45.8% of patients received

gemcitabine monotherapy compared with 54.2% of patients who received combination therapy. Thus, in this respect, the patient population appears to differ to that expected to be seen in NHS clinical practice in England although it should be noted that [redacted] of patients in the NAPOLI-1 trial only received gemcitabine as an adjuvant or neo-adjuvant treatment. Clinical advice to the ERG is that gemcitabine monotherapy is more commonly used in the adjuvant setting and gemcitabine combination therapy is more commonly used in the neo-adjuvant setting.

Previous use of gemcitabine monotherapy versus combination therapy could reflect performance status (PS) to some extent. In the NHS, patients offered combination therapy are likely to have a good PS. As a KPS of ≥70 was required for trial entry, this could in part explain why there was a greater proportion of patients treated with gemcitabine combination therapy than with monotherapy. It could also be a reason why [redacted] of patients in the NAPOLI-1 trial received the study drug as a third-line or later treatment, this is a higher proportion than would be expected to be treated in NHS clinical practice.

The higher proportion of patients treated with gemcitabine combination therapy than monotherapy in NAPOLI-1 could simply be a result of different treatment practices in the countries involved in the trial. In particular, it is noted that nab-paclitaxel in combination with gemcitabine is now commonly used outside of England but is not recommended by NICE for treating patients with metastatic pancreatic cancer in England.

The company states that, overall, the baseline patient characteristics were similar across treatment arms. The ERG agrees with this assessment but notes slight imbalances between treatment groups with regards to the site of metastatic lesions and KPS.

Patients in the 5-FU/LV arm were more likely to have metastatic lesions in sites other than the pancreas compared with patients in the nal-iri+5-FU/LV arm. In particular, more patients in the 5-FU/LV arm had metastatic lesions in the “other” category of metastatic sites than patients in the nal-iri+5-FU/LV arm (32.8% versus 23.1%). The proportion of patients with a baseline KPS 90 was higher in the nal-iri+5-FU/LV arm than in the 5-FU/LV arm, but the opposite was the case in terms of KPS 80 (KPS 90, 43.6% versus 33.6%; KPS 80, 32.5% versus 42.9%). Taken together, the differences in the site of the lesion and the greater proportion of patients with KPS 90 in the 5-FU/LV arm could suggest patients were less fit than those in the nal-iri+5-FU/LV arm although the ERG recognises there is a large degree of subjectivity in determining PS. Furthermore, it is noted that the proportion of patients with KPS ≤70 (i.e. the least fit) were similar between arms (8.6% versus 8.4%).

Table 6 Baseline characteristics of the NAPOLI-1 trial – ITT population

Characteristic	Nal-iri+5-FU/LV (n=117)	5-FU/LV (n=119)
Gender, n (%)		
• Female	48 (41.0)	52 (43.7)
• Male	69 (59.0)	67 (56.3)
Race, n (%)		
• American Indian or Alaska Native	0	0
• Asian	34 (29.1)	36 (30.3)
• Black or African American	4 (3.4)	3 (2.5)
• White	72 (61.5)	76 (63.9)
• Other	7 (6.0)	4 (3.4)
Age, years, mean (SD)	63.2 (9.06)	61.0 (9.46)
BMI, kg/m^2, mean (SD)	23.33 (4.134)	23.57 (5.054)
KPS, n (%)		
• 50	1 (0.9)	0
• 60	2 (1.7)	0
• 70	7 (6.0)	10 (8.4)
• 80	38 (32.5)	51 (42.9)
• 90	51 (43.6)	40 (33.6)
• 100	18 (15.4)	17 (14.3)
Albumin, g/dL, mean (SD)	3.97 (0.459)	3.98 (0.506)
Measurable lesions, n (%)	113 (96.6)	114 (95.8)
Measurable metastatic lesions, n (%)	97 (82.9)	103 (86.6)
Location of metastatic lesions, n (%)		
• Distant lymph node	32 (27.4)	31 (26.1)
• Liver	75 (64.1)	83 (69.7)
• Lung	36 (30.8)	36 (30.3)
• Pancreas	75 (64.1)	72 (60.5)
• Peritoneal	28 (23.9)	32 (26.9)
• Regional lymph node	13 (11.1)	14 (11.8)
• Other	27 (23.1)	39 (32.8)
Previous anti-cancer therapy, n (%)		
• Gemcitabine alone	53 (45.3)	55 (46.2)
• Gemcitabine combination	64 (54.7)	64 (53.8)
• Fluorouracil-based	50 (42.7)	52 (43.7)
• Irinotecan-based	12 (10.3)	17 (14.3)
• Platinum-based	38 (32.5)	41 (34.5)

BMI=body mass index; ITT=intent-to-treat; KPS=Karnofsky performance score; SD=standard deviation
Source: CS, Table 14

Overall, the ERG is satisfied that the treatment groups are relatively well balanced. The patient population in the NAPOLI-1 trial was generally similar to the population that is likely to be considered for treatment with nal-iri+5-FU/LV in clinical practice in England, aside from previous gemcitabine use and the usual caveat that only suitably fit patients are recruited to clinical trials, so the trial population may be slightly younger and fitter than the population seen in clinical practice.

4.2.4 Statistical approach adopted for the conduct and analysis of NAPOLI-1

In this section, the ERG provides a description and critique of the statistical approach adopted to analyse data collected during the NAPOLI-1 trial in relation to the outcomes stipulated in the NICE scope. Information relevant to the statistical approach taken by the company has been extracted from the CSR,[29] the trial statistical analysis plan (TSAP),[30] the trial protocol (version 2.2)[31] and the CS.

Trial population

The various trial populations used to analyse efficacy and safety outcomes are defined in Box 3.

Box 3 Definitions of trial populations in the NAPOLI-1 trial

- **Intent-to-treat (ITT) population**: all randomised patients, as defined by the confirmation of a successful allocation of a randomisation number through interactive web response system (IWRS). This population was the primary population for all efficacy parameters unless otherwise stated
- **Safety population**: patients that received at least one dose (including partial dose) of study medication. All safety analyses were performed on this population
- **Per protocol (PP) population**: patients who received treatment for at least 6 weeks and did not violate any inclusion/exclusion criteria nor significantly deviate from the protocol, including significant deviations in study drug administration
- **Evaluable patient (EP) population for tumour response**: all randomised and treated patients who ml inclusion/exclusion criteria, had measurable disease at baseline and were evaluable for response, i.e. patients with at least one tumour evaluation while on treatment and those with early (≤12 weeks) disease progression, including symptomatic deterioration and death
- **Tumour marker response evaluable (TMRE) population**: patients who had CA19-9 >30 U/mL at baseline
- **Clinical benefit response evaluable (CBRE) population**: patients who met at least one of the following criteria: baseline pain intensity ≥20 (out of 100); baseline morphine consumption ≥10 mg/day oral morphine equivalents; baseline KPS of 70–90 points
- **Patient-reported outcomes (PRO) population**: all ITT patients that provided baseline and at least one subsequent assessment on the EORTC-QLQ-C30 instrument
- **Pharmacokinetic (PK) population**: all treated patients with at least one PK assessment

Efficacy outcomes

The definitions and methods of analysis for the primary and secondary efficacy outcomes from the NAPOLI-1 trial are listed in Table 7. For OS, PFS, TTF and ORR, the company presents results for the ITT population and results are fully reported for the PP and EP populations for PFS, TTF and ORR in the CS and CSR. The ERG is satisfied that all

outcomes were pre-specified in the TSAP and that all outcomes were fully reported in the CSR.

In addition to the outcomes reported in Table 7, the company also reported on tumour marker response and clinical benefit rate. Additional information on these outcomes is reported in the Appendices of this ERG report in Section 11.1.

Table 7 Analysis strategy for NAPOLI-1 trial efficacy end points specified in the NICE scope

Endpoint	Definition	Statistical method	Population used for analysis
Primary outcome			
OS	Defined as the time from the date of patient randomisation to the date of death or the date last known alive	OS was compared using un-stratified log-rank tests. KM analyses were performed for each arm to obtain non-parametric estimates of the OS function and median OS. 95% CIs were computed using the log-log method. Un-stratified Cox PH regressions were used to estimate HRs and 95% CIs	ITT
Secondary outcomes			
PFS	Time from the date of patient randomisation to the date of death or disease progression, whichever occurred earlier. PFS was based on tumour and disease progression assessments per investigator according to RECIST guidelines v1.1	PFS was compared using un-stratified log-rank tests. KM analyses were performed for each arm to obtain non-parametric estimates of the PFS function and median PFS. 95% CIs were computed using the log-log method. Un-stratified Cox PH regressions were used to estimate HRs and 95% CIs	ITT, PP, EP
TTF	Defined as the time to discontinuation of treatment for any reason, including disease progression, toxicity, and death	TTF was compared using un-stratified log-rank tests. KM analyses were performed for each arm to obtain non-parametric estimates of the TTF function and median TTF. 95% CIs were computed using the log-log method. Cox PH regressions were used to estimate HRs and 95% CIs	ITT, PP, EP
ORR	Defined by the percentage of patients with a best overall response of CR or PR as assessed by the investigator from randomisation until progression or end of study, and as defined by RECIST guidelines v1.1	The 95% CI for the proportion experiencing objective response was calculated based on the normal approximation. ORRs were pairwise compared using Fisher's exact tests	ITT, PP, EP

CI=confidence interval; CR=complete response; EP=evaluable patient for tumour response; HR=hazard ratio; ITT=intent-to-treat; KM=Kaplan-Meier; KPS=Karnofsky performance score; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PH=proportional hazards; PP=per protocol; PR=partial response; RECIST=response evaluation criteria in solid tumours; TTF=time to treatment failure
Source: CS Sections 4.3.4, 4.4.3 and 4.4.4

Outline of analyses

It was planned that the primary analysis would take place once 305 deaths had occurred. The efficacy and safety data presented in the CS are from this primary analysis, which was performed using a data cut-off point of 14 February 2014.

The company highlights that there have also been some updated results for OS, PFS and ORR presented as a poster and abstract with a data cut-off date of 25 May 2015 after 378 OS events.[32]

In March 2016, a final analysis of the NAPOLI-1 trial data set was performed as all patients included in the trial had died by this time. The March 2016 results for OS and PFS were used to inform the company's cost effectiveness analysis (see Section 5.3.4).

Cox proportional hazard modelling

The analyses carried out by the company to generate OS, PFS, and TTF hazard ratios (HRs) were conducted using Cox PH modelling. The validity of this method relies on the hazards of the two comparative drugs being proportional. The company mentions in the CS (Section 4.10.1.1) that the K-M curves for the NAPOLI-1 trial OS data cross, indicating that the PH assumption is unlikely to hold. This potential violation of PH casts doubt on the validity of the generated HRs for OS.

As part of the clarification process, the ERG requested details of any testing of the PH assumption that was carried out by the company. In response, the company tested the PH assumption for the NAPOLI-1 trial OS data and provided results of the test for various analysis populations (see Appendices to this ERG report, Section 11.2). For the ITT population (analysed using un-stratified log-rank tests), the test rejected the null hypothesis that the PH assumption is valid (p=0.0169). The results of the ERG's own analyses of the OS data are in agreement with those of the company.

As the company did not report any test of the PH assumption for PFS or TTF, the ERG carried out its own testing of the PFS and TTF data from the NAPOLI-1 trial (see Appendices to this ERG report, Section 11.3.1) and found the PH assumption to be violated for both outcomes. Consequently, the ERG is of the opinion that HRs are not an appropriate measure of survival benefit for nal+iri+5-FU/LV versus 5-FU/LV.

ERG assessment of statistical approach

A summary of the checks made by the ERG in relation to the statistical approach adopted by the company to analyse data from the NAPOLI-1 trial is provided in Table 8. Having carried out these checks, the ERG is satisfied with the statistical approach employed by the company, with the exception of the violation of the PH assumption for OS, and the lack of testing of PH for PFS and TTF.

Table 8 ERG assessment of statistical approach used to analyse the NAPOLI-1 trial data

Component	Statistical approach	ERG comments
Sample size calculation	Provided in the CSR (page 74). The sample size calculation was adjusted to account for the introduction of a third treatment, in order to take into consideration that some patients would have been randomised under protocol version 1 to either nal-iri monotherapy or 5-FU/LV, and that the remainder of patients would be randomised to one of three treatment groups, nal-iri monotherapy, 5-FU/LV, or nal-iri+5-FU/LV	The ERG is satisfied with the approach taken by the company to calculate sample size, and the adjustments made to the sample size calculation after protocol version 2
Protocol amendments	A third treatment arm, nal-iri+5-FU/LV, was added to the study, as described in Section 4.2.2 of this ERG report. Other protocol amendments are provided in the CS (pages 51 to 52)	The ERG is satisfied with the company's justification for introducing a third treatment arm Other amendments were carried out prior to analysis being conducted. Therefore, they are unlikely to have been driven by the results of the trial and are not a cause for concern
Changes in planned analyses	The company outlines changes in the planned analyses in the CS (pages 55-56). In particular, the definition of the PP population was modified to require a minimum exposure threshold during the first 6 weeks of treatment of at least 80% of the planned dose. Requiring patients to receive doses as planned through 6 weeks removed patients who could not tolerate treatment early on, as well as patients who failed treatment (PD or death) before adequate dosing during the first 6 weeks could be completed	The ERG notes that the number of patients included in the PP population was fairly small, and consequently explored the reasons for exclusion from the PP population (see Section 4.2.6)
Sensitivity analyses for OS	The CS (pages 53 to 54) states the following sensitivity analyses were carried out for OS on the ITT population (except where indicated): • Log-rank test comparisons of treatments on the safety population • Log-rank test comparisons of treatments on the PP population • Stratified log-rank analyses, using randomisation stratification factors (with HR estimates from stratified Cox model) • Wilcoxon pairwise comparisons of treatments • Log-rank test comparisons of treatments with OS censored at the date any post-treatment anti-cancer therapy is first administered • Cox regression model with a time-dependent covariate to account for post-baseline therapy • Cox regression model with stepwise selection of model terms (p-value to enter <0.25, p-value to remain <0.15)	The ERG asked the company to provide results for some of the pre-specified sensitivity analyses as part of the ERG clarification letter to the company, which the company provided in their response. All other sensitivity analyses were fully reported in the CS and CSR
Subgroup analyses for OS	Provided in the CSR (page 123)	The ERG is satisfied that all subgroup analyses were pre-specified in the TSAP and were fully reported in the CSR
AEs	Safety was assessed using several summary measures of AEs, and frequencies of AEs occurring in ≥10% of patients in any treatment group were also presented. All data were analysed and presented using the safety population (CS, pages 55 and 77)	The ERG is satisfied that the results of all the AE data analyses are provided in the CSR
HRQoL	Patients were required to complete the EORTC-QLQ-C30 questionnaire at treatment start, every 6 weeks thereafter and at 30 days post follow-up. On days that the patient received the study drug, assessments were to be completed prior to study drug administration Pairwise treatment group comparisons were performed on the PRO population for each subscale using Cochran MH testing (CS, pages 50 and 55)	The ERG is satisfied that the methodology used to analyse HRQoL data is appropriate

AE=adverse event; CS=company submission; CSR=clinical study report; ERG=evidence review group; HR=hazard ratio; HRQoL=Health related quality of life; ITT=intent-to-treat; MH=Mantel-Haenszel; OS=overall survival; PP=per protocol; PRO=patient-reported outcomes; TSAP=trial statistical analysis plan
Source: CS, pages 50 to 56 and page 77 and CSR, page 123

4.2.5 Assessment of risk of bias of the NAPOLI-1 trial

The company's assessments of risk of bias presented in the CS (Table 15) are reproduced, along with ERG comments, in the Appendices to this ERG report (Section 11.4, Table 66). Overall, the ERG agrees with the company's assessments and considers that the trial was of reasonable quality. The ERG considers that the greatest risks of bias occur from the fact that the NAPOLI-1 trial was an open-label trial. This may explain why a much larger proportion of patients withdrew from the 5-FU/LV arm (13/119, 10.9%) before being treated than from the nal-iri+5-FU/LV arm (2/117, 1.7%). It is possible that patients recruited to the 5-FU/LV arm may have withdrawn from the trial upon being told that they had been randomised to receive the control treatment. Indeed, the reason for withdrawal given for 11 of the 14 (78.6%) patients in the 5-FU/LV arm who did not receive any study treatment was "subject decision". The open-label nature of the NAPOLI-1 trial may also have introduced bias into the assessment of disease progression, favouring nal-iri+5-FU/LV over 5-FU/LV. There is no independent assessment of disease progression. The company highlights that blinding of study treatment was not feasible due to different dosing schedules in the different arms. The ERG recognises the company's assertion that, as a result of the new RECIST 1.1 guidelines,[33] central independent confirmation of objective tumour response is no longer required for RCTs that do not have tumour response as their primary endpoint since it is considered that the control arm serves as an appropriate means to interpret data.

As highlighted in Section 3.3 of this report, the dosing schedule for 5-FU/LV in the nal-iri+5-FU/LV arm was different to that used in the 5-FU/LV arm. However, as argued by the company, the ERG considers it is highly unlikely that this created a bias in favour of the nal-iri+5-FU/LV arm, since the planned and recorded dose intensities of 5-FU were higher in the control arm.

4.2.6 Results from the NAPOLI-1 trial

As reported in Section 4.2.4, both the company and the ERG agree that the PH assumption is violated for the OS data. The ERG's calculations indicated that the PH assumption is also violated for PFS and TTF (Appendices to this ERG report, Section 11.3.1). For this reason, the ERG has not interpreted the HRs that are presented for these outcomes in the CS, as the HRs were calculated assuming that the PH assumption is valid.

Primary efficacy outcome

The results of the primary analysis of OS for the ITT population performed using a data cut-off point of 14 February 2014 are provided in Table 9. Median OS was longer for nal-iri+5-FU/LV patients in comparison to 5-FU/LV patients (6.1 months versus 4.2 months). The

company states that the difference in median OS between treatment groups is statistically significant. However, the company has tested this difference using the log-rank test, which relies on the PH assumption. As previously discussed, the PH assumption is invalid for OS data from NAPOLI-1, and it is therefore not possible to use the results of the log-rank test to demonstrate statistical significance in terms of median OS.

Table 9 Overall survival in the NAPOLI-1 trial – ITT population

	Nal-iri+5-FU/LV (n=117)	5-FU/LV (n=119)
Median OS, months (95% CI)	6.1 (4.76 to 8.87)	4.2 (3.29 to 5.32)
HR (95% CI; p-value)	0.67 (0.49 to 0.92; p=0.0122)	
Died, n (%)	75 (64.1)	80 (67.2)
Reason for censoring, n (%)		
Alive	37 (31.6)	27 (22.7)
Lost to follow-up	1 (0.9)	1 (0.8)
Consent withdrawn from follow-up	4 (3.4)	11 (9.2)

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; OS=overall survival
Source: CS, Table 16 and company response to the ERG clarification letter, Table 8

Interim results with a data cut-off of 25th May 2015 were in accordance with the results from the primary efficacy analysis, median OS was found to be 6.2 months (95% CI: 4.8 to 8.4) for nal-iri+5-FU/LV compared with 4.2 months (95% CI: 3.3 to 5.3) for 5-FU/LV. The company also presents median OS results from the final data cut (March 2016); these results are [redacted] to the interim results presented in the CS.

The ERG notes that a larger percentage of patients in the 5-FU/LV arm received no study treatment compared to patients in the nal-iri+5-FU/LV arm; results from the ITT population may therefore be biased in favour of the nal-iri+5-FU/LV arm. Therefore, the ERG considers that it is important to take into account the results of the sensitivity analysis of OS (Table 11) that use the safety population (including only patients who received at least one dose of study medication).

The ERG also notes that in both arms of the trial, a relatively high proportion of patients received subsequent therapy on disease progression. This may reflect the fact that, as is common in clinical trials, patients in the trial were younger and fitter than those treated in clinical practice. Relatively similar proportions of patients received subsequent therapy in some trials of oxaliplatin+5-FU/LV (see Section 4.7). There was however no treatment crossover, i.e. no patient in the 5-FU/LV arm subsequently received either nal-iri monotherapy or nal-iri+5-FU/LV. Furthermore, the types of treatment received following progression were similar between arms. Therefore, whilst it is possible that subsequent treatment prolonged OS, it is unlikely that it resulted in bias favouring one arm over another.

The details of subsequent treatments received by patients in each arm are shown in Table 10.

Table 10: Post-treatment anti-cancer therapy in the NAPOLI-1 trial

	Nal-iri+5-FU/LV (n=117)	5-FU/LV (n=119)
Received post-treatment anti-cancer therapy, n (%)*	42 (35.9)	50 (42.0)
Gemcitabine-based	11 (9.4)	14 (11.8)
5-FU-based	28 (23.9)	35 (29.4)
Irinotecan-based	10 (8.5)	12 (10.1)
Platinum-based	24 (20.5)	24 (20.2)
Other non-investigational agents	14 (12.0)	12 (10.1)
Investigational	5 (4.3)	4 (3.4)
No record of post-treatment anti-cancer therapy, n (%)	75 (64.1)	69 (58.0)

*Subjects who received therapy in combination are counted in more than one therapy category.
Source: Company response to the ERG clarification letter, adapted from Table 26

Sensitivity analyses of the primary efficacy outcome

The results of the sensitivity analyses of OS are provided in Table 11. Median OS was longer for patients in the nal-iri+5-FU/LV arm than patients in the 5-FU/LV arm for all analyses. The ERG notes that in the safety population, results were almost identical to those presented for the ITT population. Therefore, it seems that despite the fact a larger percentage of patients in the 5-FU/LV arm did not receive any study treatment in comparison to the nal-iri+5-FU/LV arm, bias has not been introduced.

Median OS times were considerably longer for both treatment groups in the PP population in comparison to the ITT population (2.8 months OS gain in the nal-iri+5-FU/LV arm and 0.9 months OS gain in the 5-FU/LV arm). However, the number of patients in the PP population was relatively small, indicating that only 56% of the nal-iri+5-FU/LV arm (66/117 patients) and 60% of the 5-FU/LV arm (71/117) received treatment for at least 6 weeks and did not violate any inclusion/exclusion criteria nor significantly deviate from the protocol. Nevertheless, the findings of the analysis using the PP population were in accordance with the analyses using the ITT and safety populations in that they demonstrated a beneficial effect of nal-iri+5-FU/LV in comparison to 5-FU/LV in terms of median OS.

Table 11 Sensitivity analyses of overall survival in the NAPOLI-1 trial

Sensitivity analysis	Nal-iri+5-FU/LV	5-FU/LV
Stratified analysis on ITT population		
N	117	119
Median OS, months (95% CI)	6.1 (4.76 to 8.87)	4.2 (3.29 to 5.32)
HR (95% CI; p-value)¶	0.57 (0.41 to 0.80; p=0.0009)	
Safety population		
N	117	105
Median OS, months (95% CI)	6.2 (4.86 to 8.87)	4.2 (3.29 to 5.29)
HR (95% CI; p-value)	0.66 (0.48 to 0.91; p=0.0108)	
PP population		
N	66	71
Median OS, months (95% CI)	8.9 (6.44 to 10.5)	5.1 (3.98 to 7.16)
HR (95% CI; p-value)	0.57 (0.37 to 0.88; p=0.0106)	
ITT population (censoring at change in therapy)		
N	117	119
Median OS, months (95% CI)	6.1 (4.70 to 12.68)	4.0 (3.06 to 5.88)
HR (95% CI; p-value)	0.5665 (0.39 to 0.83; p=0.0033)	

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; OS=overall survival; PP=per protocol
¶For the stratified analysis on the ITT population, the p-values are derived from the two-sided stratified log-rank test, incorporating randomisation strata; HRs are derived using the stratified Cox proportional hazards model with treatment as the independent variable.
Source: CS, Table 17 and company response to the ERG clarification letter, Table 10

During the clarification process, the ERG requested a breakdown of reasons why patients from the ITT population of the NAPOLI-1 trial were not included in the PP analysis; the company's response is provided in Table 12. The information in Table 12 highlights that by far the most common reason for exclusion from the ITT population was "insufficient dosing" of study treatment in the nal-iri+5-FU/LV arm and a combination of insufficient dosing or not receiving the dose at all in the 5-FU/LV arm. As noted in Table 8 of this ERG report, the PP population was modified to require a minimum exposure threshold during the first 6 weeks of treatment of at least 80% of the planned dose and therefore insufficient dosing is presumed by the ERG to relate to patients who did not receive 80% of the planned dose. The company notes that requiring patients to receive doses as planned through 6 weeks removed patients who could not tolerate treatment early on, as well as patients who failed treatment (progressed or died) before adequate dosing during the first 6 weeks could be completed. However, given median OS was considerably longer for both treatment groups in the PP population than in the ITT population (2.8 months OS gain in the nal-iri+5-FU/LV arm and 0.9 months OS gain in the 5-FU/LV arm), patients in the NAPOLI-1 trial may have experienced considerably more treatment benefit had they been able to tolerate at least 80% of the planned dosing.

Table 12 Reasons for excluding patients from the PP population for overall survival in the NAPOLI-1 trial

	Nal-iri+5-FU/LV (N=117)	5-FU/LV (N=119)
Patients excluded from the ITT population, n (%)	51 (43.6)	48 (40.3)
Reason, n (%)		
Did not meet eligibility criteria: adequate hepatic function	1 (0.9)	1 (0.8)
Enrolled with Vater-Papilla tumour	0	1 (0.8)
Insufficient dosing	47 (40.2)	31 (26.1)
Insufficient evidence of distal metastases	1 (0.9)	1 (0.8)
Not dosed	2 (1.7)	13 (10.9)
Randomised to 5-FU/LV, treated with nal-iri+5-FU/LV	0	1 (0.8)

ITT=intent-to-treat; PP=per protocol
Source: company response to the ERG clarification letter, Table 6

Finally, as part of the clarification process, the ERG requested the results of several sensitivity analyses that were pre-specified in the TSAP. The company provided these results (see Appendices to this ERG report, Section 11.5). The results of the sensitivity analyses suggested that nal-iri+5-FU/LV statistically significantly improved OS in comparison to 5-FU/LV alone.

Subgroup analyses of the primary efficacy outcome

The company performed subgroup analyses for OS in order to examine the robustness of the overall treatment effect across pre-specified subgroups of prognostic factors. The subgroups for which analyses were conducted are reported in Table 13.

The results of these subgroup analyses are provided in the CSR (pages 123-124). They suggest that the treatment effect [redacted] nal-iri+5-FU/LV [redacted] 5-FU/LV [redacted]. However, the ERG notes that the number of patients in each of these [redacted] and the study was not [redacted] effects and therefore the results of these analyses [redacted]. The ERG does not consider any of the results of the subgroup analysis to suggest that there any obvious subgroups of patients who shouldn't be given nal-iri+5-FU/LV. However, clinical advice to the ERG is that patients who had received prior irinotecan are unlikely to be considered for nal-iri+5-FU/LV since they have already been exposed to non-liposomal irinotecan.

Table 13 Pre-planned subgroups for overall survival sensitivity analyses in the NAPOLI-1 trial

Factor	Subgroup Levels
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Source: CSR, Table 7-17

Progression-free survival

The results of the primary analysis of PFS for the ITT population performed at the data cut-off point of 14 February 2014 are provided in Table 14. Median PFS was longer for patients treated with nal-iri+5-FU/LV than for patients treated with 5-FU/LV (3.1 months versus 1.5 months). The company states that the difference in median PFS between treatment groups is statistically significant. However, as explained in Section 4.2.4 of this ERG report, the PH assumption is invalid for PFS data and, therefore, it is not appropriate to use the results of the log-rank test to assess statistical significance in terms of median PFS.

Table 14 Progression-free survival) in the NAPOLI-1 trial – ITT population

	Nal-iri+5-FU/LV (n=117)	5-FU/LV (n=119)
Median PFS, months[†] (95% CI)	3.1 (2.69 to 4.17)	1.5 (1.41 to 1.84)
HR (95% CI; p-value)[§]	0.56 (0.41 to 0.75; p=0.0001)	
Progressed n (%)	65 (55.6)	59 (58.0)
Died n (%)	18 (15.4)	23 (19.3)
Reason for censoring n (%)		
Clinical deterioration	3 (2.6)	2 (1.7)
Last non-PD assessment within 12 weeks of cut-off date	15 (12.8)	7 (5.9)
Not treated and no post-baseline tumour assessment	1 (0.9)	10 (8.4)
Other	15 (12.8)	8 (6.7)

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; PD=progressive disease; PFS=progression-free survival
[†]Median PFS is the K-M estimate of the median PFS time. [§]HRs are derived from the un-stratified Cox proportional hazards model with treatment as the independent variable. P-values are derived from the two-sided un-stratified log-rank test
Source: CS, Table 18 and company response to the ERG clarification letter, Table 8

Interim results with a data cut-off of 25th May 2015 were in accordance with the results from the primary efficacy analysis, median PFS was found to be 3.1 months (95% CI: 2.7 to 4.2) for nal-iri+5-FU/LV compared with 1.5 months (95% CI: 1.4 to 1.8) for 5-FU/LV. The company also presents median PFS results from the final data cut (March 2016); these results are [redacted] to the interim results presented in the CS.

Sensitivity analyses: progression-free survival

The results of the sensitivity analyses of PFS are provided in Table 15. Median PFS was longer for patients in the nal-iri+5-FU/LV arm than in the 5-FU/LV arm for all analyses. Median PFS time was considerably longer for nal-iri+5-FU/LV in the PP population in comparison to the ITT population (1.2 months PFS gain). As with OS, this demonstrates the extent of benefit that patients receiving nal-iri+5-FU/LV can experience if they are able to tolerate the study drug for 6 weeks at ≥80% of the planned dose.

Table 15 Sensitivity analyses of progression-free survival in the NAPOLI-1 trial

Sensitivity analysis	Nal-iri+5-FU/LV	5-FU/LV
Stratified analysis on ITT population		
N	117	119
Median PFS, months (95% CI)	3.1 (2.69 to 4.17)	1.5 (1.41 to 1.84)
HR (95% CI; p-value)[¶]	0.51 (0.37 to 0.70; p<0.0001)	
PP population		
N	66	71
Median PFS, months (95% CI)	4.3 (3.06 to 5.72)	1.6 (1.41 to 2.60)
HR (95% CI; p-value)	0.46 (0.31 to 0.67; p<0.0001)	
Evaluable population		
N	104	92
Median PFS, months (95% CI)	3.1 (2.66 to 4.21)	1.4 (1.41 to 1.81)
HR (95% CI; p-value)	0.53 (0.39 to 0.72; p<0.0001)	
ITT population (early discontinuation)		
N	117	119
Median PFS, months (95% CI)	3.1 (2.66 to 4.14)	1.4 (1.41 to 1.68)
HR (95% CI; p-value)	0.55 (0.41 to 0.74; p<0.0001)	
ITT population (missing data)		
N	117	119
Median PFS, months (95% CI)	3.1 (2.69 to 4.17)	1.5 (1.41 to 1.84)
HR (95% CI; p-value)	0.56 (0.41 to 0.75; p=0.0001)	
ITT population (progression directly derived from lesion data)		
N	117	119
Median PFS, months (95% CI)	3.3 (2.66 to 4.21)	1.4 (1.41 to 1.84)
HR (95% CI; p-value)	0.56 (0.41 to 0.76; p=0.0001)	

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; PFS=progression-free survival; PP=per protocol
[¶]For the stratified analysis on the ITT population, the p-values are derived from the two-sided stratified log-rank test, incorporating randomisation strata; HRs are derived using the stratified Cox proportional hazards model with treatment as the independent variable
Source: CS, Table 19 and company response to the ERG clarification letter, Table 10

Time to treatment failure

The results of the analysis of TTF for the ITT population are provided in Table 16. Median TTF was longer for nal-iri+5-FU/LV patients in comparison to 5-FU/LV patients (2.3 months versus 1.4 months).

Table 16 Time to treatment failure in the NAPOLI-1 trial – ITT population

	Nal-iri+5-FU/LV (n=117)	5-FU/LV (n=119)
Median TTF, months (95% CI)	2.3 (1.58 to 2.79)	1.4 (1.31 to 1.41)
HR (95% CI; p-value)	0.60 (0.45 to 0.78; p=0.0002)	
Progressed, n (%)	61 (52.1)	65 (54.6)
Died, n (%)	1 (0.9)	5 (4.2)
Other reason for treatment termination (n (%))	41 (35.0)	43 (36.1)

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; TTF=time to treatment failure
Source: CS, Table 20 and company response to the ERG clarification letter, Table 8

Sensitivity analyses: time to treatment failure

The results of the sensitivity analyses of TTF are provided in Table 17. The results of the sensitivity analyses were in accordance with the results of the primary analysis of TTF; median TTF was longer for patients in the nal-iri+5-FU/LV arm than for patients in the 5-FU/LV arm for both sets of sensitivity analyses.

Table 17 Sensitivity analyses of time to treatment failure in the NAPOLI-1 trial

Sensitivity analysis	Nal-iri+5-FU/LV	5-FU/LV
PP population		
N	66	71
Median TTF, months (95% CI)	4.1 (2.79 to 5.53)	1.4 (1.41 to 2.43)
HR (95% CI; p-value)	0.49 (0.34 to 0.71; p=0.0001)	
Evaluable population		
N	104	92
Median TTF, months (95% CI)	2.5 (1.68 to 2.89)	1.4 (1.35 to 1.45)
HR (95% CI; p-value)	0.58 (0.43 to 0.78; p=0.0004)	

CI=confidence interval; HR=hazard ratio; PP=per protocol; TTF=time to treatment failure
Source: CS, Table 21 and company response to the ERG clarification letter, Table 10

Objective response

The results for objective response for the ITT population are provided in Table 18. The ORR was found to be statistically significantly higher for patients in the nal-iri+5-FU/LV arm in comparison to patients in the 5-FU/LV arm.

Table 18 Objective response in the NAPOLI-1 trial – ITT population

	Nal-iri+5-FU/LV (n=117)	5-FU/LV (n=119)
Best overall response, n (%)		
Partial response	9 (7.7)	1 (0.8)
Stable disease[†]	47 (40.2)	26 (21.8)
Non-complete response/non-progressive disease	3 (2.6)	2 (1.7)
Progressive disease	35 (29.9)	56 (47.1)
Not evaluable[¶]	23 (19.7)	34 (28.6)
Objective response rate[¶]		
N	9	1
Rate, % (95% CI)	7.69 (2.86 to 12.52)	0.84 (0.0 to 2.48)
Rate difference (95% CI)	6.85 (1.75 to 11.95)	
p-value[§]	0.0097	

CI=confidence interval; ITT=intent-to-treat; RECIST= response evaluation criteria in solid tumours
[†]Designation of stable disease required at least one assessment of stable disease according to RECIST v1.1 criteria at least 6 weeks after starting treatment
[¶]Subjects with insufficient data for response classification were classified as not evaluable for best overall response, and as a non-responder for objective response in the ITT population.
[§]Two-sided p-values from pairwise Fisher's exact test
Source: CS, Table 22

4.3 *Approach to identifying and assessing the quality of evidence to include in an ITC*

4.3.1 Company's approach to deriving an ITC

As noted in Section 4.2.1, the company identified 13 RCTs (16 publications) for inclusion into its systematic review. To determine whether it was possible to compare nal-iri+5-FU/LV with a comparator that is more relevant to NHS clinical practice than 5-FU/LV, the company undertook a NMA feasibility assessment; this assessment is described in the clinical effectiveness text of the CS (Section 4.10.1). The company considered the network of evidence formed by 12 of these RCTs (as in one trial[34] not all patients had received gemcitabine previously) and presented network diagrams summarising the identified evidence in the CS (Figure 6). The company considered that evidence from three trials (NAPOLI-1, CONKO-003 and PANCREOX) could, theoretically, be included in an ITC to generate evidence for the effectiveness of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV. The network of evidence used in the ITC is shown in Figure 1.

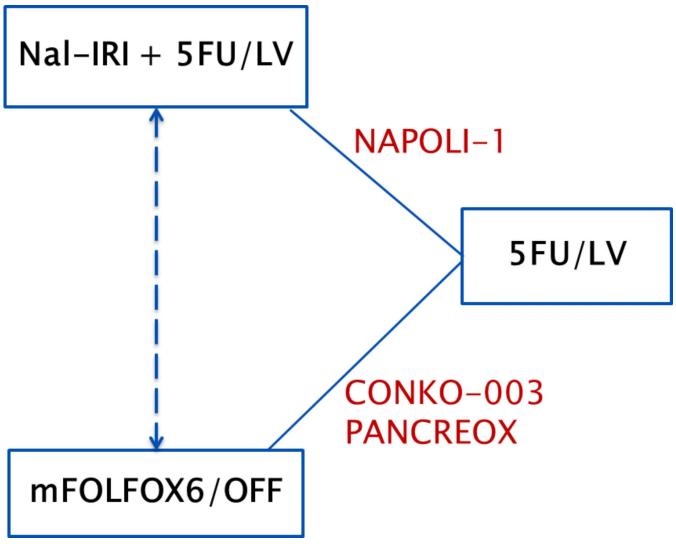

Figure 1 ITC network: Combining NAPOLI-1, CONKO-003 and PANCREOX

Source: CS, Figure 14

The company provides several reasons why the trials are not homogeneous, and therefore why it is inappropriate to include these trials in an ITC. These reasons are presented, along with ERG comments, in Table 19. The company concludes that the conduct of an ITC was considered "unfeasible".

Advice to the company from a panel of three KOLS considered that it was difficult to determine if trials were similar because:

- potentially relevant information is not consistently provided for all three trials
- it is difficult to identify treatment effect modifying variables due to the severity of disease and the complexity of treatment regimens.

The KOLS concluded that combining data from the three trials in an ITC might be considered flawed and "naïve". Thus the company states that an ITC was not conducted because a NMA was deemed "unfeasible".

However, the company considered that results from an ITC were necessary to allow the cost effectiveness of nal-iri+5-FU/LV to be compared with oxaliplatin+5-FU/LV (NHS standard of care), and thus an ITC was undertaken. The Bucher adjusted indirect comparison method[35] was used to undertake the ITC. Results from the ITC are provided, in the form of PFS and OS HRs, in the cost effectiveness section of the CS (CS, Table 39, p104).

Importantly, the company highlights that, upon inspection of the K-M curves:

- the NAPOLI-1 trial OS K-M curves cross and therefore the PH assumption for OS is not likely to hold
- the PFS K-M curves cross in both the CONKO-003 trial and in the PANCREOX trial, meaning that the PH assumption for PFS is not likely to hold within/between trials.

Table 19 Company assessment of comparability of trials included in the ITC

Parameter	Issue	ERG comment
Trial characteristics		
Study location	Not comparable: • NAPOLI-1 – multinational • CONKO-003 – Germany • PANCREOX – Canada	The ERG agrees. Trial location is a possible source of heterogeneity within the network
Follow-up	Follow-up duration not reported for the NAPOLI-1 and PANCREOX trials	The ERG notes that in the poster that reports the PANCREOX trial, follow-up duration is reported to be 4 months. Follow-up duration remains unknown for NAPOLI-1, which the ERG considers to be unlikely as the company conducted this trial and ought to have access to this information Nevertheless, the ERG notes that follow-up durations differ considerably between PANCREOX (4 months) and CONKO-003 trial (54.1 months), and that this introduces heterogeneity into the network
5-FU/LV treatment	Inconsistent reporting of treatment details means that it is difficult to comment on the comparability of dosing	The ERG disagrees. The treatment regimens are adequately reported, although information relating to the PANCREOX trial is only available online from the ClinicalTrials.gov trial register website Although there are differences between trials in terms of the oxaliplatin+5-FU/LV regimens and the 5-FU/LV monotherapy regimens, the ERG does not consider there is any evidence to suggest that these differences in regimens lead to differences in efficacy. The ERG therefore, considers that the

Parameter	Issue	ERG comment
		different regimens of oxaliplatin+5-FU/LV may be considered to be of similar efficacy, and similarly, the different regimens of 5-FU/LV may be considered to be equally efficacious
Prior treatment	Inconsistent prior treatments: • NAPOLI-1 – any prior gemcitabine combination therapy • CONKO-003 – prior gemcitabine monotherapy • PANCREOX – prior gemcitabine therapy (unclear whether monotherapy or in combination)	The ERG agrees that prior treatment is a possible source of heterogeneity within the network
Patient characteristics		
Patient age	Median age of patients was 62 years in the CONKO-003 and NAPOLI-1 trials, and 65 years in the PANCREOX trial	The ERG disagrees this is a source of heterogeneity and considers median age is sufficiently similar across trials (range: 61 in 5-FU/LV arm of the CONKO-003 trial to 67 in PANCREOX trial).
Other patient characteristics	Inconsistent reporting of ECOG PS, CA19-9 levels and number of metastatic sites	The ERG agrees that due to inconsistent reporting, it is not possible to assess whether there is heterogeneity with regards to these patient characteristics
Outcomes		
PFS	PH assumption is not likely to hold within the CONKO-003 and PANCREOX trials	The ERG agrees that the PH assumption is violated for the CONKO-003 and PANCREOX trials. ERG analyses indicate that PH is also violated for NAPOLI-1 PFS data See Section 4.3.2 of this ERG report for ERG assessment of PH issues
OS	PH assumption is not likely to hold in the NAPOLI-1 trial	Results of analyses conducted by the ERG indicate that the PH assumption is violated for the NAPOLI-1, CONKO-003 and PANCREOX trials. See Section 4.3.2 of this ERG report for ERG assessment of PH issues
Response rate	NAPOLI-1 was the only trial to report both the objective response rate and CA19-9 response	The ERG agrees with the company.

ECOG=Eastern Co-operative Oncology Group; OS=overall survival; PFS=progression-free survival; PH=proportional hazards; PS=performance status
Source: CS, pages 72 to 73

4.3.2 ERG's critique of the company's ITC

The ERG considers that the company's systematic review to identify trials that could be used as sources of evidence for an ITC was appropriately undertaken and that the most relevant trials were identified. The ERG also broadly agrees with the company's assessment of bias in these trials (see Appendices to this ERG report, Section 11.4). In addition, the ERG is in general agreement with the company about the limitations of the clinical effectiveness evidence used in the network, namely trial heterogeneity and violation of PH assumptions.

The ERG has carried out additional work to assess the validity of the PH assumptions that need to hold for the results of the ITC to be reliable. The PH assumption within trials is best assessed by considering H-H plots. This type of plot shows the relationship between the

cumulative hazard for each trial event at common time points in two trial arms. These plots were created to assess the proportionality of patient OS and PFS experience using K-M data from the nal-iri+5-FU/LV and 5-FU/LV arms of the NAPOLI-1 trial and by digitising published K-M data from the two arms of the CONKO-003 and PANCREOX trials. For an assumption of PH to be valid, two criteria must be met:

- the data should follow a straight line trend, with individual data points randomly distributed close to, and on either side, of a trend line
- the linear trend line should pass through the graph origin (zero value on both axes), i.e. the intercept component of the linear regression model should be zero.

Results from the ERG's analyses are summarised in Table 20.

Table 20 Summary of findings of analyses undertaken by the ERG to assess proportional hazards

Trial	OS		PFS	
	Linear trend?	Intercept value	Linear trend?	Intercept value
NAPOLI-1 trial	No	N/A	No, except for later stages when proportionality appears reasonable	-0.121 (95% CI: -0.189 to -0.052, p<0.001)
CONKO-003 trial	Only appears supported after about 7.5 months	-0.141 (95% CI: -0.187 to -0.096, p<0.0001)	No	N/A
PANCREOX trial	Appears reasonable	+0.073 (95 %CI: 0.039 to 0.106, p<0.0001)	No	N/A

In addition, for results from the ITC to be reliable, PFS and OS data for 5-FU/LV within the three trials (NAPOLI-1, CONKO-003 and PANCREOX) should be equivalent (i.e. can be assumed to exhibit a HR of 1.0). An examination of data from the three trials shows that this assumption is not valid.

Full details of the analyses conducted by the ERG to investigate PH in the ITC are presented in the Appendices to this ERG report (Section 11.3.2).

4.3.3 ERG's conclusions on the credibility of results of the company's ITC

The ERG considers that the findings from the ITC are not reliable, due to the heterogeneity of the trials and because the necessary PH assumptions (OS and PFS) are not met. It is therefore not possible to derive a credible estimate of clinical or cost effectiveness for nal-iri+5-FU/LV compared with oxaliplatin+5-FU/LV.

4.4 Safety

Safety data for nal-iri+5-FU/LV and 5-FU/LV are reported for the NAPOLI-1 trial safety population. Safety data from the NAPOLI-1 trial for nal-iri monotherapy are also presented in the CS (but not examined in detail in this ERG report). The CS does not include any comparison of AE data between nal-iri+5-FU/LV and oxaliplatin+5-FU/LV, oxaliplatin+capecitabine or capecitabine monotherapy; however, in Appendix 4.3 of the CS the company presents some AE data for oxaliplatin+5-FU/LV from the CONKO-003 and PANCREOX trials. The ERG has compared AEs across these two trials, two other RCTs which include treatment with oxaliplatin+5-FU/LV (the SWOG S1115 trial[36] of mFOLFOX6 without bolus 5-FU and the Yoo trial[17] of mFOLFOX) and the NAPOLI-1 trial in Section 4.7. A comparison of AEs reported for nal-iri monotherapy between the NAPOLI-1 trial and NCT00813163 is presented by the ERG in Appendices to this ERG report (Section 11.8).

4.4.1 Adverse events reported in NAPOLI-1

A summary of the incidence of aggregated AEs is provided in Table 21. While the proportion of treatment emergent AEs (TEAEs) was similar across both arms (nearly all patients experienced a TEAE in the trial), all other types of AEs were reported less frequently in the 5-FU/LV arm than in the nal-iri+5-FU/LV arm. The majority of AEs in all arms were treatment-related, particularly in the nal-iri+5-FU/LV arm where approximately 90% of all TEAEs were treatment-related, compared with approximately 70% for patients treated with 5-FU/LV.

The company highlights that the primary reasons for dose delay with nal-iri+5-FU/LV arm were myelosuppression, particularly neutropenia, and decreased neutrophil count. The ERG observes that another notable AE resulting in dose delay in the nal-iri+5-FU/LV arm was a [redacted] (see Appendices to this ERG report, Section 11.6.1). Myelosuppression was also cited as the main reason for dose reduction for patients receiving nal-iri+5-FU/LV, alongside gastrointestinal disorders (see Appendices to this ERG report, Section 11.6.2). Gastrointestinal disorders and infections and infestations were the primary reasons cited by the company for discontinuation of treatment with nal-iri+5-FU/LV (Appendices to this ERG report, Section 11.6.3).

Table 21 Summary of adverse events in the NAPOLI-1 trial – safety population

Adverse event n (%)	Nal-iri+5-FU/LV (n=117)	5-FU/LV (n=134)
≥1 TEAE	116 (99.1)	132 (98.5)
≥1 TR-TEAE	107 (91.5)	93 (69.4)
≥1 CTCAE grade 3 or higher TEAE	90 (76.9)	75 (56.0)
≥1 CTCAE grade 3 or higher treatment-related TEAE	63 (53.8)	24 (17.9)
≥1 serious TEAE	56 (47.9)	60 (44.8)
≥1 TEAE leading to any dose modification	83 (70.9)	48 (35.8)
• ≥1 TEAEs resulting in dose delay	72 (61.5)	43 (32.1)
• ≥1 TEAE leading to dose reduction	39 (33.3)	5 (3.7)
• ≥1 TEAE leading to dose discontinuation	13 (11.1)	10 (7.5)
≥1 TR-TEAE leading to any dose modification		
• ≥1 TR-TEAE resulting in dose delay	59 (50.4)	19 (14.2)
• ≥1 TR-TEAE leading to dose reduction	35 (29.9)	3 (2.2)
• ≥1 TR-TEAE leading to dose discontinuation	5 (4.3)	2 (1.5)

CTCAE=common terminology criteria for adverse events; TEAE=treatment-emergent adverse event; TR-TEAE=treatment-related treatment-emergent adverse event
Source: CS, adapted from Table 30 and company response to ERG clarification letter, Table 17

TEAEs that were very common (≥10%) are summarised in Appendices to this ERG report (Section 11.7, Table 73). AEs that were very common (≥10%) in patients treated with nal-iri+5-FU/LV and occurred at a higher frequency (≥5%) than in the 5-FU/LV arm were as follows: diarrhoea (59.0% versus 26.1%), vomiting (52.1% versus 26.1%), nausea (51.3% versus 34.3%), decreased appetite (44.4% versus 32.1%), fatigue (40.2% versus 27.6%), anaemia (37.6% versus 23.1%), pyrexia (23.1% versus 11.2%), neutropenia (23.1% versus 3.0%), weight decreased (17.1% versus 6.7%), neutrophil count decreased (14.5% versus 1.5%), white blood cell count decreased (14.5% versus 1.5%), alopecia (13.7% versus 4.5%), stomatitis (13.7% versus 6.0%), mucosal inflammation (10.3% versus 3.7%) and platelet count decreased (10.3% versus 2.2%).

Serious TEAEs are summarised by the company in Appendix 6, Table 8, of the CS. The most common (>3%) serious TEAEs for patients treated with nal-iri+5-FU/LV were vomiting (11.9%), diarrhoea (6.0%), abdominal pain (4.3%), nausea (3.4%) and sepsis (3.4%); the most common serious TEAE (>3%) for patients treated with 5-FU/LV was abdominal pain (4.5%).

Treatment-emergent deaths that were attributed to AEs were similar in the nal-iri+5-FU/LV arm (2.6%) and the 5-FU/LV arm (2.2%). One death (0.9%) was assessed as being related to treatment in the nal-iri+5-FU/LV arm with no deaths assessed as being attributable to treatment in the 5-FU/LV arm.

A safety comparison with patients heterozygous for *UGT1A1*28* was difficult to perform because of the small number of patients in this subgroup ([redacted]

[redacted]). However, the company reports that no large differences in the frequency or severity of TEAEs were detected. Nonetheless, the ERG observes that the draft summary of product characteristics (SmPC) highlights that individuals who are homozygous for *UGT1A1*28* are at [redacted].

Although not presented in the CS, the ERG also notes from the draft SmPC that [redacted] have been described. [redacted] However, the incidence of [redacted] among [redacted] compared to [redacted] was reported in [redacted] compared to [redacted]. It is noted in the SmPC that this is consistent with [redacted] that showed a [redacted].

4.4.2 Overall comment on safety with nal-iri+5-FU/LV

The company states that, overall, the safety profile of nal-iri+5-FU/LV is consistent with prior experience with nal-iri, and with the safety profiles of irinotecan and 5-FU/LV. Despite some apparent differences in the incidences of some AEs for nal-iri monotherapy in the NAPOLI-1 trial compared with the incidences of some AEs for nal-iri monotherapy NCT00813163, the ERG agrees with this assessment.

It is further noted by the company that despite a higher incidence of neutropenia overall with nal-iri+5-FU/LV than with nal-iri monotherapy, more frequent and severe gastrointestinal AEs were observed in the nal-iri monotherapy arm. This, it is argued, suggests that the more frequent administration of nal-iri, with a lower dose, results in fewer and less severe gastrointestinal AEs.

4.5 Health related quality of life

In the CS, HRQoL data are reported for the nal-iri+5-FU/LV and 5-FU/LV arms of the NAPOLI-1 trial.

4.5.1 Primary evidence for health related quality of life

The evaluation of HRQoL was conducted using data from the NAPOLI-1 trial PRO population, which only included ITT patients who had completed the EORTC-QLC-C30 questionnaire at baseline and on at least one subsequent occasion: nal-iri+5-FU, [redacted]; 5-

FU: [redacted]; (CSR, Table 7-2). The EORTC QLQ-C30 questionnaire consists of 15 subscales in three independent domains: Global Health Status; Functional Scale Score (physical, role, emotional, cognitive, and social functioning); and Symptom Scale Score (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties).

Patients were required to complete the EORTC-QLQ-C30 questionnaire at the start of treatment, every 6 weeks thereafter and at 30 days post follow-up. On days that the patient received the study drug, the questionnaire was completed prior to study drug administration.

Baseline EORTC-QLQ-C30 scores were similar between treatment arms for all domains: for Global Health Status, scores were above the midpoint of the scale; for Functional Scale, the scores were high (≥75) indicating a high/healthy level for functioning; and for Symptom Scale, the scores were noted to be between 0 and 33 for all symptoms, indicating low levels of symptomatology. Findings over time were reported at 6 weeks and 12 weeks. No appreciable changes in Global Health Status or Functional Scale were reported, suggesting there were no negative effects on HRQoL from treatment, as measured by these scales. A similar finding was reported for most of the subscales within the Symptom Scale, with the exception of nausea and vomiting, and diarrhoea. For both arms, the baseline score on the nausea and vomiting subscale was 0 (indicating no symptomology). This score [redacted] in the nal-iri+5-FU+LV arm but [redacted] at 6 weeks and was [redacted] at 12 weeks. The diarrhoea scale also had a baseline score of 0 in both arms, [redacted] in the nal-iri+5-FU/LV arm [redacted] in the 5-FU/LV arm at 6 weeks [redacted] in the nal-iri+5-FU/LV [redacted] at 12 weeks.

4.5.2 Q-TWiST analysis

As supportive evidence, the company also undertook a quality adjusted time without symptoms or toxicity (Q-TWiST) analysis as described by Revicki 2006 (page 412).[37] This involved partitioning total survival in the ITT population over 12 months into: time with AE grade ≥3 toxicity (TOX); time in relapse after disease progression (REL); and time without symptoms or AE grade ≥3 toxicity (TWiST). Mean Q-TWiST was then calculated by multiplying the time spent in each health state by its respective utility (0.5 for TOX, 0.5 for REL and 1.0 for TWiST).

The results from the Q-TWiST are summarised in Table 22. Time in TOX favoured 5-FU/LV over nal-iri+5-FU/LV by 0.7 months, there was little difference between arms for time in REL (marginally favouring 5-FU/LV) and TWiST favoured nal-iri+5-FU/LV by 1.0 months. The company reported the TWiST gain to be statistically significant. Overall, nal-iri+5-FU/LV

patients had a 1.3 months (95% CI: 0.4 to 2.1) greater Q-TWiST (range threshold analyses: 0.9 to 1.6 months), with a relative Q-TWiST gain of 24% (range threshold analyses: 17% to 31%).

Table 22 Results from the Q-TWiST analysis in the NAPOLI-1 trial – ITT population

Health state	Utility	Nal-iri+5-FU/LV (n=117)		5-FU/LV (n=119)	
		Months	Score	Months	Score
TOX: Time with AE grade ≥3 toxicity	0.5	1	0.5	0.3	0.15
REL: Time in relapse after disease progression	0.5	2.5	1.25	2.7	1.35
TWiST: Time without symptoms or AE grade ≥3 toxicity	1	3.4	3.4	2.4	2.4
Total (Q-TWiST)			5.1		3.9

Source: CS, Section 4.7.2.6

The company also conducted a scenario analysis using data from the PP population. The results of this analysis support the results generated using ITT data. In the PP population, Q-TWiST was also reported to be significantly superior in nal-iri+5-FU/LV patients (Q-TWiST gain=1.8 months; 95% CI: 0.7 to 3.0); this gain is reported by the company to be clinically and statistically significant.

4.5.3 Overall comment on health related quality of life

Whilst, theoretically, HRQoL data are useful, the ERG questions whether, given the relatively small number of patient responses (Table 23), the EORTC-QLQ-C30 results generated from the data collected as part of the NAPOLI-1 trial can be considered robust.

Table 23 Proportions of patients in the NAPOLI-1 trial ITT population who compled the EORTC-QLC-C30 questionnaire

Assessment	nal-iri+5-FU/LV	5-FU/LV
Baseline	[redacted]	[redacted]
12 weeks	[redacted]	[redacted]
30 days post follow-up		[redacted]

Source: CSR, adapted from Table 7-2 and Table 7-16

The company states that the results from the Q-TWiST analysis show that treatment with nal-iri+5-FU/LV results in statistically significant and clinically important gains in quality-adjusted survival compared with treatment with 5-FU/LV. The ERG notes that although some differences in Q-TWiST scores are described as being statistically significant, no p-values are reported in the CS although confidence intervals, presented for these estimates at ASCO 2016 by Pelzer (and reported by the ERG in Section 4.5.2), appear to show statistical significance. In addition, it is noted that the authors of the Revicki 2006 study[37] suggest that a difference in Q-TWiST scores of 10% to 15% is clinically important; in the PRO population of the NAPOLI-1 trial, a Q-TWIST score of 24% is reported (range threshold analyses: 17%

to 31%), suggesting that the results are clinically important. However, the ERG notes that the results of the Q-TWiST analyses are not presented in the CSR and so appear to be a post-hoc exploratory analysis; the findings should therefore be treated with caution.

4.6 Efficacy evidence from non-randomised study (NCT00813163)

The ERG considers that the efficacy findings from the NCT00813163 study are of limited relevance to the decision problem. However, as noted in Section 4.2.3, the ERG has noted that the proportion of patients treated with gemcitabine monotherapy and combination therapy may have some impact on efficacy if the choice of prior therapy also reflects patient fitness especially if a greater proportion of patients receiving prior combination therapy reflects a fitter patient population. It is interesting to note, therefore, that in the NCT00813163 study, there was a greater proportion of patients with worse PS (25% with KPS ≤70) compared with patients in the NAPOLI-1 trial (~9%) despite a higher proportion of patients having been previously treated with combination therapy (77.5% compared with ~55%). However, median OS and PFS for patients treated with nal-iri monotherapy in the NCT00813163 study (5.2 and 2.4 months respectively) was similar to that reported in the nal-iri monotherapy arm of the NAPOLI-1 trial (4.9 and 2.7 months respectively). More information on the NCT00813163 study is described in Appendices to this ERG report (Section 11.8).

4.7 Additional work on clinical effectiveness undertaken by the ERG

As highlighted previously (Sections 2.2.2 and 3.3 of this ERG report), oxaliplatin+5-FU/LV regimens are the most common regimens used for treating patients with metastatic pancreatic cancer previously treated with gemcitabine. Oxaliplatin+5-FU/LV is, therefore, considered by the ERG to be the standard of care, and the most appropriate comparator to nal-iri+5-FU/LV. As methodological issues precluded the conduct of an ITC, and since the company did not present safety data for oxaliplatin+5-FU/LV, the ERG presents a narrative summary of the efficacy and safety of nal-iri+5-FU/LV alongside that of oxaliplatin+5-FU/LV. The ERG's approach is pragmatic and enables crude comparisons across RCTs to be undertaken to determine if results obtained in the NAPOLI-1 trial differ markedly to results obtained in other RCTs. The obvious limitation of the approach is that it is impossible to reach reliable conclusions about relative effectiveness, particularly as trial populations may differ. It is not possible to derive a quantitative estimate but it is possible to explore (qualitatively) the similarity and differences of trial results, and the extent to which these may be attributed to differences in trial and patient characteristics.

4.7.1 Trial characteristics

Trial characteristics are summarised in Table 24. Alongside nal-iri+5-FU/LV, different types of oxaliplatin+5-FU/LV regimens are considered: OFF in CONKO-003, mFOLFOX6 in the PANCREOX trial, mFOLFOX6 without bolus 5-FU in the SWOG S1115 trial and mFOLFOX in the trial conducted by Yoo. The NAPOLI-1 trial is the only multinational trial, the other trials were conducted in Germany, Canada, US and South Korea respectively. The NAPOLI-1 trial is also the largest trial (n=266) and the Yoo trial of mFOLFOX is the smallest (n=61). In all of the trials, patients had received prior gemcitabine but the extent to which this was monotherapy and/or combination therapy varied widely; only 9.8% of patients received monotherapy in the trial of mFOLFOX reported by Yoo, compared to 100% of patients receiving OFF in the CONKO-003 trial. Trial follow-up periods differed considerably across trials (where reported) from a planned follow-up of 4 months in the PANCREOX trial of mFOLFOX6 to a median follow-up of 54.1 months in the CONKO-003 trial of OFF. The dates of recruitment spanned 11 years from 2004 to 2015. The earliest of the trials to be completed was the CONKO-003 trial of OFF (2007) and the most recent trial to be completed was the phase II SWOG S1115 trial of mFOLFOX6 without bolus 5-FU (2015).

Table 24 Characteristics of randomised controlled trials which investigated nal-iri+5-FU/LV or oxaliplatin+5-FU/LV

Characteristic	NAPOLI-1	CONKO-003	PANCREOX	SWOG S1115	Yoo
Design	Phase III, open-label RCT	Phase III, open-label RCT	Phase III, open-label RCT	Phase II, open-label RCT	Phase II, open-label RCT
Recruited, n (dates)	n=266* (2012 to 2013)	n=168 (2004 to 2007)	n=108 (2010 to 2013)	n=120 (2012 to 2015)	n=61 (2007 to 2008)
Follow-up	Not known	54.1 months (median)	4 months (reported in methods)	Every 6 months for up to 3 years (reported in methods)	5.6 months (median)
Country	Multi-centre, multinational trial: North America (20 sites), Europe (30 sites), Asia (12 sites), South America (8 sites) and Oceania (6 sites)	Germany, 16 centres	Canada, 15 centres	US, 534 centres	Asian Medical Center, Seoul, Korea
Intervention	Nal-iri + 5-FU/LV, every 2 weeks: 80 mg/m^2 nal-iri, 400 mg/m^2 LV over 30 minutes, followed by 2400 mg/m^2 5-FU over 46 hours on Day 1	OFF every 4 weeks:† 85 mg/m^2 oxaliplatin on Days 8 and 22, 200 mg/m^2 LV on Days 1, 8, 15 and 22, 5-FU 2,000 mg/m^2 over 24 hours on Days 1, 8, 15 and 22 2 week of rest before next cycle of treatment	mFOLFOX6, every 2 weeks: 85 mg/m^2 oxaliplatin (given as a 2-hour infusion), 400 mg/m^2 LV (given as a 2-hour infusion simultaneous to oxaliplatin), 400 mg/m^2 dose of 5-FU given as bolus followed by 2400 mg/m^2 continuous infusion over 46 hours on Day 1	mFOLFOX6 (without bolus 5-FU) every 2 weeks: 85 mg/m^2 oxaliplatin (given as a 2-hour infusion) and continuous 5-FU over 46hours on Day 1 (no detail about 5-FU dose or administration of LV given)	mFOLFOX every 2 weeks: 85 mg/m^2 oxaliplatin (given as a 2-hour infusion), 400 mg/m^2 LV and 2,000 mg/m^2 5-FU IV over 46hours on Days 1
Comparator	5-FU + LV (6 weekly cycle): LV at a dose of 200 mg/m^2 over 30 minutes followed by 2,000 mg/m^2 5-FU over 24 hours administered on Days 1, 8, 15 and 22 2 week of rest before next cycle of treatment	5-FU + LV (6 weekly cycle):† 200 mg/m^2 LV followed by 2,000 mg/m^2 5-FU over 24 hours on Days 1, 8, 15 and 22 2 week of rest before next cycle of treatment	5-FU + LV (6 weekly cycle): 400 mg/m^2 LV (given as a 2-hour infusion) and 400 mg/m^2 dose of 5-FU given as bolus followed by 2400 mg/m^2 continuous infusion over 46 hours on Day 1	Selumetinib (AZD-6244) + the Akt inhibitor MK-2206: 100 mg AZD-6244 daily on days 1 to 28 plus MK2206 daily on Days 1 to 28 .	mFOLFIRI.3 every 2 weeks: 70 mg/m^2 irinotecan (over 1 hour), 400 mg/m^2 (over 2 hours) and 2000 mg/m^2 5-FU (over 46 h) from Day 1 and another 70 mg/m^2 irinotecan (over 1 hour) at the end of the 5-FU infusion
Previous treatment	Gemcitabine therapy (monotherapy: 45.8% or combination: 54.2%)	First-line gemcitabine monotherapy (100%)	Gemcitabine therapy	Gemcitabine therapy (1-line but no more than 1-line)	Gemcitabine-based1st-line therapy (monotherapy 9.8% or combination 91.2%)

IV=intravenous; KPS=Karnofsky Performance Status; RCT=randomised controlled trial
* NAPOLI-1 was a three-armed trial comparing nal-iri+5-FU/LV with 5-FU/LV and nal-iri monotherapy with 5-FU/LV. Data reported here are for patients in the former comparison
† Included best supportive care according to current palliative care guidelines, i.e. including anti-infective treatment, psychological counselling as needed, biliary stenting or drainage (if indicated), nutritional advice, pain management, and nutritional supplementation

4.7.2 Patient characteristics

Patient characteristics are summarised in Table 25. Across the trials, with the exception of the trial of mFOLFOX reported by Yoo in which the median age of patients was 55, the median age was relatively similar across the trial arms of interest (ranging from 62 years in the OFF arm of CONKO-003 to 65 years in the mFOLFOX6 arm of PANCREOX). A similar proportion of patients had previously had curative surgery with nal-iri+5-FU/LV in the NAPOLI-1 trial (36.1%) as with mFOLFOX in the Yoo trial (36.7%) but more patients treated with OFF in the CONKO-003 trial had had curative surgery (44.7%). At least 88% of patients had metastatic disease in any given trial, and relatively similar proportions of patients treated with nal-iri+5-FU/LV in the NAPOLI-1 trial had liver metastasis (64.1%) as those treated with mFOLFOX6 without bolus 5-FU in the SWOG S1115 trial (62.9%); in the Yoo trial, the proportion of patients with liver metastasis treated with mFOLFOX was slightly greater (70.0%). Body mass index was also similar in the two trials that reported this measure (the NAPOLI-1 trial of nal-iri+5-FU and the PANCREOX trial of mFOLFOX6), being approximately 23 kg/m^2. A comparison of the duration of previous gemcitabine therapy was difficult because not all of the trials reported this measure and where they did, it was not reported consistently. However, the median duration of previous gemcitabine therapy was much higher in the NAPOLI-1 trial for nal-iri+5-FU arm (22.1 months) than in the OFF arm of the CONKO-003 trial (4.6 months).

The most notable difference across trials appeared to relate to baseline PS. In particular, 59.0% of patients treated with nal-iri+5-FU/LV in the NAPOLI-1 trial, 53.9% of patients treated with OFF in the CONKO-003 trial and 45.0% of patients treated with mFOLFOX6 without bolus 5-FU in the SWOG S1115 trial had KPS ≥90 or ECOG PS 0, whereas the proportions of patients with ECOG PS 0 treated with mFOLFOX6 in PANCREOX and with mFOLFOX in Yoo were 13.0% and 16.7% respectively. The mFOLFOX6 arm of the PANCREOX trial and mFOLFOX arm of the Yoo trial also included patients with ECOG PS 2: 11.1% and 3.3% respectively.

Table 25 Participant characteristics of randomised controlled trials which investigated nal-iri+5-FU/LV or oxaliplatin+5-FU/LV

Characteristic	NAPOLI-1		CONKO-003		PANCREOX		SWOG S1115		Yoo	
Regimen	Nal-iri + 5-FU/LV (n=117)	5-FU/LV (n=119)	OFF (n=76)	5-FU/LV (n=84)	mFOLFOX6 (n=54)	5-FU/LV (n=54)	mFOLFOX6 (n=62)	AZD-6244 + MK-2206 (n=58)	mFOLFOX (n=30)	mFOLFORI.3 (n=31)
Age, median (Range) years	63 (41, 81)	62 (34, 80)	62 (37, 83)	61 (43, 78)	65 (38, 82)	67 (48, 78)	66 (34, 83)	69 (54, 88)	55 (35, 69)	55 (37, 73)
Sex (% male)	59.0	56.3	52.6	57.1	57.4	55.6	35.5	60.3	66.7	77.4
% Metastatic	100	100	88.2	88.1	92.6	94.4	100	100	--	--
% Liver metastases	64.1	69.7	--	--	--	--	62.9	74.1	70.0	61.3
Duration of advanced disease, median months	6.9	6.2	--	--	7.9	5.7	--	--	--	--
% Performance status	KPS ≥90: 59.0 80: 32.5 ≤70: 8.6	KPS ≥90: 47.9 80: 42.9 ≤70: 8.4 Missing: 0.8	KPS ≥90: 53.9 ≤80: 46.1	KPS ≥90: 47.6 ≤80: 52.4	ECOG 0: 13.0 1: 75.9 2: 11.1	ECOG 0: 18.9 1: 75.5 2: 5.7	ECOG* 0: 45.0 1: 55.0	ECOG* 0: 41.5 1: 58.5	ECOG 0: 16.7 1: 80.0 2: 3.3	ECOG 0: 16.1 1: 83.9 2: 0
Albumin, g/dL, mean	3.97 (0.46)	3.98 (0.51)	--	--	--	--	≥3 (eligibility criteria)		>3 (eligibility criteria)	
BMI, median (range), kg/m^2	Mean (SD): 23.33 (4.13) Min, max 16.0, 43.5	Mean (SD): 23.57 (5.05) Min, max 16.7, 42.9	--	--	23.7 (18.1, 37.7)	24.3 (16.5, 53.9)	--	--	--	--
% Curative surgery	34.2	36.1	44.7	32.1	--	--	--	--	36.7	32.3
Duration of previous gemcitabine, median (range), months	22.1 (0.1, 129.3)	21.4 (2.1, 147.9)	4.6 [95% CI: 3.8 to 6.0]†	5.3 [95% CI: 4.4 to 6.0]†	--	--	≤ 4 months: 37.1%	≤ 4 months: 37.9%	--	--

-- Not reported; BMI=body mass index; ECOG= Eastern Cooperative Oncology Group; KPS=Karnofsky performance Status; SD=standard deviation
*Results for PS only reported in poster presentation which included 115 patients (mFOLFOX6, n=60, AZD-6244 + MK-2206, n=55)
† CONKO-003 also reports data < 3months (27.6% versus 25.0%), 3 to 6 months (32.9% versus 38.1%) and >6months (39.5% versus 36.9%)

4.7.3 Efficacy outcomes

Key efficacy findings are summarised in Table 26.

Three of the RCTs investigating oxaliplatin+5-FU/LV (the CONKO-003 trial, the PANCREOX trial and the SWOG S1115 trial) report an OS of between 5.9 months and 6.7 months. These results are similar to those reported for nal-iri+5-FU/LV in the NAPOLI-1 trial (6.1 months). The trial reported by Yoo, however, reports a less impressive OS for mFOLFOX of only 3.4 months.

RCTs investigating oxaliplatin+5-FU/LV report a PFS of 2.9 months for OFF in the CONKO-003 trial and between 2.0 months and 3.1 months for mFOLFOX6 (without and with bolus in the SWOG S1115 trial and PANCREOX trial respectively). These results are similar to those reported for nal-iri+5-FU/LV in the NAPOLI-1 trial (3.1 months). The trial reported by Yoo, however, reports a less impressive PFS for mFOLFOX of only 1.4 months.

Response rates appeared to be generally similar in two of the trials of oxaliplatin+5-FU/LV (the SWOG S1115 trial of mFOLFOX6 without bolus 5-FU and the Yoo trial of mFOLFOX) of approximately 7%, which compare to 9% for patients treated with nal-iri+5-FU/LV in the NAPOLI-1 trial. In all three of these trials, the best response was a partial response. In the PANCREOX trial of mFOLFOX6, response rates in both arms appeared to be much higher than any other trial, ranging from 8.8% for patients treated with 5-FU/LV to 13.2% for patients treated with mFOLFOX6. However, it is not stated how many responses were complete responses (if indeed any).

The proportion of patients who received subsequent treatment on disease progression could also impact on OS, although it should be noted that there are currently no proven third-line treatment options available. Nonetheless, it is noticeable that, from a comparison of the 5-FU/LV arms, the higher the proportion of patients who received subsequent therapy, the higher the median OS reported. A similar picture emerged for oxaliplatin+5-FU/LV with the exception of the mFOLFOX6 arm of the PANCREOX trial, which had much fewer patients who received subsequent therapy than in any other trial.

Alternatively, a higher proportion of patients receiving subsequent treatment can be indicative of a higher proportion of patients who are fitter at that point in time and, therefore, more likely to receive additional treatment. There does not appear to be any apparent relationship between the proportion who received subsequent treatment and the proportion of patients with ‘better’ PS at baseline (KPS ≥90 or ECOG PS 0).

Table 26 Key efficacy findings reported from randomised controlled trials of patients with metastatic pancreatic cancer treated with nal-iri+5-FU or oxaliplatin+5-FU/LV and who were all previously treated with gemcitabine

Endpoint	NAPOLI-1		CONKO-003		PANCREOX		SWOG S1115		Yoo	
	Nal-iri + 5-FU/LV (n=117)	5-FU/LV (n=119)	OFF (n=76)	5-FU/LV (n=84)	mFOLFOX6 (n=54)	5-FU/LV (n=54)	mFOLFOX6 (n=62)	AZD-6244 + MK-2206 (n=58)	mFOLFOX (n=30)	mFOLFORI.3 (n=31)
OS, months	6.1 (4.76, 8.87)	4.2 (3.29, 5.32)	5.9	3.3	6.1	9.9	6.7 (6.0, 8.3)	3.9 (3.5, 4.6)	3.4 *	3.8 *
HR (95% CI)	0.67 (0.49 to 0.92)		0.66 (0.48 to 0.91)		1.78 (1.08 to 2.93)		--		--	
12-month OS, n (%)	-- (26)	-- (16)	15 (19.7)	11 (13.1)	--	--	--	--	--	--
PFS, months	3.1 (2.69 to 4.17)	1.5 (1.41 to 1.84)	2.9*	2.0*	3.1	2.9	2.0 (1.8, 2.9)	1.9 (1.8, 2.1)	1.4 *	1.9 *
HR (95% CI)	0.56 (0.41 to 0.75)		0.68 (0.50 to 0.94)*		1.00 (0.66 to 1.53)		--		--	
ORR (%)	7.7	0.8	--	--	13.2	8.5	6.5	0	7	0 †
Additional therapy on progression (%)	37.1	42.0	28.9 ‡	21.4 ‡	Chemo-therapy: 6.8	Chemo-therapy: 23.1	53 ¥	35 ¥	Crossover: 23.3 §	Crossover: 38.7 §

CI=confidence interval; HR=hazard ratio; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

-- Not reported

Note: 12-month OS reported in appendices to CS and taken from K-M curve in CONKO-003 (figure 3), rate for NAPOLI-1 is only given in the text of the summary to the CS

* Data reported in weeks in published paper

† The trial authors state that objective response could not be ascertained in the mFOLFIRI.3 arm

¥ Based on population of patients reported in the conference poster (n=60 and n=55)

§ After disease progression to a stage at which a salvage regimen was required, a crossover to the alternate protocol was undertaken by 12 patients (39%) in the mFOLFIRI.3 arm and by 7 (23%) in the mFOLFOX arm. The median time to crossover to the alternate treatment was 8.3 weeks (range 3.3 to 18.1 weeks) in the mFOLFIRI.3 arm, and 15 weeks (range 7.0 to 32.6 weeks) in the mFOLFOX arm

‡ Paper reports: Of these, seven patients (32%) in the OFF arm were treated with taxanes, and 13 patients (72%) in the 5-FU/LV arm received oxaliplatin-based chemotherapy

Note data for NAPOLI-1 reported above are from initial analysis, 14 February 2014 (consistent with all data for clinical effectiveness reported in the clinical effectiveness sections of the CS and this ERG report)

4.7.4 Safety findings

Key AEs reported across trials are summarised in Table 27. The reporting of AEs was not consistent. It is unclear if the AEs reported in the CONKO-003 trial and PANCREOX trial were TEAEs or treatment-related and so are assumed by the ERG to be TEAEs. For the NAPOLI-1 trial, the AEs presented in Table 27 are TEAEs. As highlighted in Section 4.4, the majority of AEs in this trial were treatment-related. In the SWOG S1115 trial and in Yoo, all AEs were reported to be treatment-related.

The incidence of treatment-related neutropenia with mFOLFOX in Yoo, both all-grade (48.2%) and grade ≥3 (20.7%), was much higher than the proportion of TEAEs reported with nal-iri+5-FU/LV in NAPOLI-1 (23.1% and 14.5% respectively; treatment-related neutropenia is not reported in the CS but from Table 14.3.1.6 of the CSR, it is evident that [redacted] cases of [redacted] associated with nal-iri+5-FU/LV [redacted]). There was also a much greater proportion of patients with grade 3 to 4 neutropenia reported with mFOLFOX6 in the PANCREOX trial (32.7%) than with nal-iri+5-FU/LV (14.5%) in the NAPOLI-1 trial. Interestingly, the SWOG S1115 trial reported no cases of treatment-related neutropenia with mFOLFOX6 without bolus 5-FU.

Diarrhoea appeared to be more common with nal-iri+5-FU/LV than with all oxaliplatin+5-FU/LV regimens. All-grade diarrhoea was 50.0% with nal-iri+5-FU/LV in the NAPOLI-1 trial compared with no more than 21.1% reported with OFF in the CONKO-003 trial. Grade ≥3 diarrhoea was 12.8% with nal-iri+5-FU/LV in the NAPOLI-1 trial, compared with no more than 6.5% with mFOLFOX6 without bolus 5-FU in the SWOG S1115 trial. However, rates of vomiting appeared to be relatively similar between nal-iri+5-FU/LV and all oxaliplatin+5-FU/LV regimens. All-grade rates of vomiting were either slightly greater with OFF in the CONKO-003 trial (59.2%) or slightly lower with mFOLFOX in the Yoo trial (48.2%) than with nal-iri+5-FU/LV in the NAPOLI-1 trial (52.1%); grade ≥3 vomiting was 11.1% with nal-iri+5-FU/LV in the NAPOLI-1 trial, compared with no more than 10.3% with mFOLFOX in the Yoo trial.

Other AEs of note identified by the company were anaemia and fatigue. The incidence of all-grade anaemia appeared to be lower with nal-iri+5-FU/LV in the NAPOLI-1 trial (37.6%) than with oxaliplatin+5-FU/LV regimens (55.2% in the Yoo trial of mFOLFOX to 60.5% in the CONKO-003 trial of OFF). However, the incidence of grade ≥3 anaemia appeared to be higher with nal-iri+5-FU/LV in the NAPOLI-1 trial (9.4%) compared with between 2.0% with mFOLFOX6 in the PANCREOX trial to 3.9% with OFF in the CONKO-003 trial. The

incidence of grade ≥3 fatigue appeared to be similar with nal-iri+5-FU/LV in the NAPOLI-1 trial (13.7%) than with oxaliplatin+5-FU/LV regimens (12.9% to 14.2%).

In the CS, the company highlights that peripheral neuropathy, a common type of neurotoxicity, is a frequent treatment-related AE for oxaliplatin-containing chemotherapy regimens. The company argues that, based on a review of colorectal cancer,[38] grade ≥2 neuropathy occurs in approximately 40% to 50% of patients. In the RCTs of oxaliplatin+5-FU/LV regimens in metastatic pancreatic cancer, the incidences of all-grade neurotoxicity and treatment-related neurotoxicity were similar (OFF in the CONKO-003 trial was 42.1% and mFOLFOX in the Yoo trial was 44.8%) to those in the aforementioned review. Grade 3 neuropathy was reported to occur in 10% to 20% of patients treated with oxaliplatin-containing chemotherapy in the aforementioned review of colorectal cancer.[38] However, grade ≥3 peripheral neuropathy was reported to be at most 4.1% mFOLFOX6 without bolus 5-FU in the SWOG S1115 trial and grade ≥3 neurotoxicity was reported by 3.9% of patients treated with OFF in the CONKO-003 trial; no incidence of grade ≥3 neurotoxicity was reported for patients treated with mFOLFOX. Clinical advice received by the ERG is that neurotoxicity generally correlates with duration of treatment so will tend to be higher for patients with colorectal cancer who are likely to stay on treatment for longer periods than patients with pancreatic cancer. When grade 2 neurotoxicity occurs, dose reductions/omissions are usually instigated to prevent worsening. In patients treated with nal-iri+5-FU/LV in the NAPOLI-1 trial, peripheral neuropathy was much less common (all grade: 1.7% and grade ≥3: 0) than reported with oxaliplatin+5-FU/LV.

In addition to data summarised in Table 27, there appear to be a similar amount of AEs leading to treatment discontinuation with nal-iri+5-FU/LV (11.1% in the NAPOLI-1 trial) as with mFOLFOX6 with or without bolus 5-FU (9.7% in the PANCREOX trial and 16.3% in the SWOG S1115 trial respectively). AEs leading to treatment discontinuation were not reported for OFF in the CONKO-003 trial or mFOLFOX in the Yoo trial. However, it is noted that in the CONKO-003 trial, a dose reduction to 75% was required in 10% of OFF administrations; 9% of planned OFF administrations were not given, and 81% of OFF administrations were full doses.

Compared with 0.9% of treatment-related deaths with nal-iri+5-FU/LV in the NAPOLI-1 trial, there were no treatment-related deaths from AEs with mFOLFOX6 in PANCREOX and 3.4% with mFOLFOX in the Yoo trial. It is not reported if there were any treatment-related deaths in the CONKO-003 trial of OFF or the SWOG S1115 trial of mFOLFOX6 without bolus 5-FU.

Table 27 Key safety findings reported from randomised controlled trials of patients with metastatic pancreatic cancer treated with nal-iri+5-FU or oxaliplatin+5-FU/LV and who were all previously treated with gemcitabine

Adverse event	NAPOLI-1		CONKO-003		PANCREOX		SWOG S1115		Yoo	
	Nal-iri + 5-FU/LV (n=117)	5-FU/LV (n=134)	OFF (n=76)	5-FU/LV (n=84)	mFOLFOX6 (n=54)	5-FU/LV (n=54)	mFOLFOX6 (n=62)	AZD-6244 + MK-2206 (n=57)	mFOLFOX (n=29)	mFOLFORI.3 (n=29)
Neutropenia, All grades, n (%)	27 (23.1)	4 (3.0)	--	--	--	--	--	--	14 (48.2)	13 (44.8)
Grade 3 to 4, n (%)	17 (14.5)	1 (0.7)	--	--	16 (32.7)	2 (3.8)	0	0	6 (20.7)	7 (24.1)
Febrile neutropenia, All grades, n (%)	[redacted]	[redacted]	--	--	--	--	--	--	0	1 (3.4)
Grade 3 to 4, n (%)	2 (1.7)	0	--	--	2 (4.1)	0	0	0	0	1 (3.4)
Diarrhoea, All grades, n (%)	69 (59.0)	35 (26.1)	16 (21.1)	19 (22.6)	--	--	--	--	5 (17.2)	12 (41.4)
Grade 3 to 4, n (%)	15 (12.8)	6 (4.5)	1 (1.3)	0	1 (2.0)	0	4 (6.5)	4 (7.0)	0	2 (6.9)
Vomiting, All grades, n (%)	61 (52.1)	35 (26.1)	45 (59.2) †	39 (46.4) †	--	--	--	--	14 (48.2)	9 (31.0)
Grade 3 to 4, n (%)	13 (11.1)	4 (3.0)	1 (1.3) †	3 (3.6) †	2 (4.1)	0	3 (4.8)	1 (1.8)	3 (10.3)	3 (10.3)
Anaemia, All grades, n (%)	44 (37.6)	31 (23.1)	46 (60.5)	54 (64.3)	--	--	--	--	16 (55.2)	15 (51.7)
Grade 3 to 4, n (%)	11 (9.4)	9 (6.7)	3 (3.9)	2 (2.4)	1 (2.0)	0	2 (3.2)	3 (5.3)	1 (3.4)	1 (3.4)
Fatigue, All grades, n (%)	47 (40.2)	37 (27.6)	--	--	--	--	--	--	--	--
Grade 3 to 4, n (%)	16 (13.7)	5 (3.7)	--	--	7 (14.2)	1 (1.9)	8 (12.9)	7 (12.3)	--	--
Neurotoxicity, All grades, n (%)	[redacted]	[redacted]	32 (42.1)	6 (7.1)	--	--	--	--	13 (44.8)	1 (3.4)
Grade 3 to 4, n (%)	[redacted]	[redacted]	N: 3 (3.9)	N: 0	PN: 2 (4.1)	PN: 0	0	0	0	0

-- Not reported; N=neuropathy; PN=peripheral neuropathy
† CONKO-003 reports nausea/emesis (vomiting) together
Note: AEs reported by Yoo were described as treatment-related AEs as were grade 3 to 5 AEs reported in SWOG S1115 while treatment-related AEs were also reported for the NAPOLI-1 trial, data here are presented for treatment emergent AE; it is unclear whether AEs reported for other trials are treatment-emergent or treatment-related but are assumed to be treatment-emergent
Data marked as CiC extracted from CSR, Table 14.3.2.7.3

4.7.5 ERG comment on efficacy and safety findings from the ERG's narrative summary of additional trial data

Overall, the trial evidence suggests that, for patients treated with nal-iri+5-FU/LV or oxaliplatin+5-FU/LV, OS is expected to be approximately 6 months and PFS approximately 2 to 3 months. The findings from the trial by Yoo suggest a lower OS and PFS but survival with oxaliplatin+5-FU/LV appears to be similar to the irinotecan regimen, FOLFORI.3. It is unclear why the findings in this trial differ so markedly to those from the other trials but this phenomenon may be related to differences in trial and baseline characteristics, namely the fact that this was the only trial conducted in a predominantly Asian population, a much larger proportion of patients who had received gemcitabine combination (as opposed to monotherapy) therapy in the past, a younger patient population, and a greater proportion of patients with ECOG PS 1. The Yoo trial is also a relatively small trial (nearly half the size of the next smallest PANCREOX trial) which may have been a contributory factor.

The ERG notes the median OS of 9.9 months reported in the 5-FU/LV arm of the PANCREOX trial, is much longer than median OS reported in the other four trials (Table 26). Without access to a fully published paper, the ERG can only speculate possible reasons for this. These include imbalances in the mFOLFOX6 arm versus the 5-FU/LV arm, namely fewer patients with ECOG PS 0 (13.0% versus 18.9%) but more with ECOG PS 2 (11.1% versus 5.7%), the greater duration of advanced disease in the mFOLFOX6 arm (7.9 months versus 5.7 months) and much fewer patients treated with mFOLFOX6 than treated with 5-FU/LV receiving subsequent chemotherapy on disease progression (6.8% versus 23.1%).

As expected, neurotoxicity, including peripheral neuropathy, was more common in patients treated with oxaliplatin+5-FU/LV than in patients treated with nal-iri+5-FU/LV. Although neutropenia is recognised as a very common AE in the population treated with nal-iri+5-FU/LV, it appears to be even more common in two trials of oxaliplatin+5-FU/LV (the PANCREOX trial of mFOLFOX6 and the Yoo trial of mFOLFOX); perhaps surprisingly, there were no cases of neutropenia reported in the SWOG S1115 trial of mFOLFOX6 without bolus 5-FU. Diarrhoea, on the other hand, does appear to be more common with nal-iri+5-FU/LV than oxaliplatin+5-FU/LV, as does anaemia.

The ERG urges caution in interpreting the findings from these crude comparisons. The results may be unreliable because of potentially important differences in trial characteristics and in patient populations and, as also noted in the CS, unreported additional potentially relevant information.

4.8 Conclusions of the clinical effectiveness section

The only trial which assesses the effectiveness of nal-iri+5-FU/LV is the NAPOLI-1 trial. This is a phase III, multi-centre, multinational, RCT comparing the intervention with 5-FU/LV. Overall, the NAPOLI-1 trial appears to be of reasonable quality; the ERG considers that there is some risk of bias from the fact that it was an open-label trial.

The patient population recruited to the NAPOLI-1 trial is, in many respects, representative of patients who would be treated for metastatic pancreatic cancer after progressing on treatment with gemcitabine in routine clinical practice in England. It is however noticeable that a greater proportion of patients had received prior gemcitabine combination therapy and fewer patients had received gemcitabine monotherapy than would be seen in NHS clinical practice in England. Furthermore, as is common with all clinical trials, the patient population was on average younger and fitter than would be seen in clinical practice, and this may explain why a relatively large proportion of patients received study treatment in the third-line (or later) setting.

Results from the trial show that, for a range of efficacy measures, including OS and PFS, nal-iri+5-FU/LV is superior to 5-FU/LV. The increase in median OS of 1.9 months reported in the NAPOLI-1 trial compared with those receiving 5-FU/LV represents a significant improvement in OS (a 45% increase in median OS compared with the median OS in the 5-FU/LV arm), likely to be of great value to both the patient and their family. Furthermore, despite an increase in TEAEs compared with 5-FU/LV, particularly in relation to myelosuppression and gastrointestinal disorders, there was no apparent deterioration in HRQoL with nal-iri+5-FU/LV.

However, in the NHS, 5-FU/LV is rarely used to treat patients with metastatic pancreatic cancer who have progressed following treatment with gemcitabine. The most common regimen currently used to treat these patients, despite the lack of a reliable evidence base to support it, is oxaliplatin+5-FU/LV (considered by the ERG to be the most common treatment in approximately 75% of cases). Capecitabine monotherapy is considered by the ERG to be the next most commonly used comparator (in 25% of cases) although differences by geographical region exist and so some clinicians also use oxaliplatin+capecitabine in a minority of cases. The company concluded that it was not feasible to conduct an ITC to compare nal-iri+5-FU with any of the comparators used in the NHS or specified in the NICE scope, although an ITC comparing nal-iri+5-FU/LV with oxaliplatin+5-FU/LV was conducted for the purposes of generating evidence to inform the company's economic evaluation. The ERG considers that the results from the ITC lack reliability as the PH assumptions required

to conduct a credible comparison were not met and there was also some evidence of heterogeneity across trials in terms of trial location, patient characteristics, prior treatment with gemcitabine (monotherapy versus combination therapy) and length of trial follow-up. Therefore, it is not possible to generate a reliable quantitative measure of the relative efficacy of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV.

Taking a pragmatic approach to comparing the effectiveness of nal-iri+5-FU/LV with oxaliplatin+5-FU/LV, the ERG undertook a crude comparison of findings across RCTs. The ERG concluded that the PFS and OS outcomes for patients treated with oxaliplatin+5-FU/LV reported in these trials are similar in magnitude to the PFS and OS outcomes of patients who were treated with nal-iri+5-FU/LV in the NAPOLI-1 trial. The ERG also compared AEs across the trials and while it is likely that treatment with nal-iri+5-FU results in more cases of diarrhoea in patients than treatment with oxaliplatin+5-FU/LV, it is likely to result in fewer cases of neutropenia or neurotoxicity. However, these findings can only be considered exploratory.

In summary, it appears that treatment with nal-iri+5-FU/LV is of greater efficacy than 5-FU/LV for patients with metastatic pancreatic cancer who have progressed on treatment with gemcitabine. Despite an increase in AEs (mostly myelosuppression and gastrointestinal disorder), there appears to be no appreciable deterioration in HRQoL for patients treated with nal-iri+5-FU compared with 5-FU/LV. However, 5-FU/LV is rarely used to treat such patients and it is impossible to say whether nal-iri+5-FU/LV is more or less clinically effective than oxaliplatin+5-FU/LV, oxaliplatin+capecitabine or capecitabine monotherapy in the population of interest.

5 COST EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by the company in support of prescribing nal-iri in combination with 5-FU/LV for the treatment of metastatic adenocarcinoma of the pancreas in adult patients who have progressed following gemcitabine based therapy.

The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has also provided an electronic copy of their economic model, which was developed in Microsoft Excel.

5.1 The company's review of cost effectiveness evidence

5.1.1 Objective of the cost effectiveness review

A systematic review was conducted to summarise findings from published cost effectiveness studies that are relevant to the decision problem. The searches were conducted on 19 January 2016. The databases searched, along with date limits, and sources that were hand searched, are listed in Table 28. Details of the search strategies employed by the company are provided in Appendix 7 of the CS.

Table 28 Data sources for economic systematic review

Search strategy component	Sources	Date limits
Electronic database searches via the OVID platform	MEDLINE® MEDLINE® In-Process & Other Non-Indexed Citations	1946 to present
	Excerpta Medical Database (Embase®)	1980 to 201, 6 week 3
	Econlit	1886 to December 2015
	The Cochrane® Library, including: Central Register of Controlled Trials (CENTRAL) Cochrane Database of systematic Reviews Database of Abstracts of Reviews of Effects (DARE) Health Technology Assessment (HTA) NHS Economic Evaluation Database (EED)	 December 2015 2005 to 13 January 2016 2nd quarter 2015 4th quarter 2015 2nd quarter 2015
Hand searching	Reference lists of included studies and relevant systematic reviews	NA
	Cost effectiveness Analysis (CEA) Registry	NR
	Research Papers in Economics (RePEc)	NR
	Conference proceedings, including: American Society of Clinical Oncology (ASCO) European Society for Medical Oncology (ESMO) International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	2013 to 2016
	Previous HTA submissions/appraisals	

HTA=health technology assessment; NA=not applicable; NR=not reported
Source: CS, p92 and CS, Appendices 7.1 and 7.4

5.1.2 Eligibility criteria used in study selection

The inclusion/exclusion criteria used to facilitate study selection are presented in Table 29.

Table 29 Eligibility criteria used in economics search strategy

	Inclusion criteria	Exclusion criteria
Population	Patients with advanced or metastatic (stage IV) pancreatic cancer who have been previously treated with gemcitabine-containing treatment at any line of therapy (including gemcitabine in non-adjuvant/adjuvant/locally advanced patients who are now diagnosed with metastatic disease)	Studies in which it is unclear whether the population meets the eligibility criteria
Interventions	Pegylated liposomal irinotecan hydrochloride trihydrate (nal-iri) in combination with 5-FU and LV	-
Comparators	Oxaliplatin in combination with 5-FU and LV (FOLFOX or OFF regimens) Capecitabine in combination with oxaliplatin Fluoropyrimidine monotherapy, including capecitabine, 5-FU† and S-1	-
Outcomes	Model perspective, time horizon and discounting Description of model or cost assumptions Summary health outcomes (e.g. QALYs, LYG) ICERs	-
Study design	CUAs Other forms of CEA will be tagged (and included if no CUAs are identified)	-
Language restrictions	English language. English language abstracts of non-English language publications will also be included	-
Date of publication	Not restricted by date	-

CEA=cost effectiveness analysis; CUA=cost utility analysis; ICER=incremental cost effectiveness ratio; LYG=life years gained; QALY=quality adjusted life years
†Including in combination with LV
Source: CS, Appendix 7, Table 10

5.1.3 Included and excluded studies

The company identified 253 papers through the electronic searches and removed 37 duplicate papers, leaving 216 titles and abstracts to be reviewed. Seven records were ordered for full paper review and all seven were excluded: four on the basis of patient population (no prior treatment) and one each for reasons of language (Japanese), intervention (none of interest) and paper type (review). The publications excluded on the basis of the full text review are detailed in Appendix 7.7 of the CS (Table 11). No publications meeting the eligibility criteria were identified via hand searches.

No relevant studies were identified by the company.

5.1.4 Findings from cost effectiveness review

The company's review identified no evidence to support the use of nal-iri in combination with 5-FU/LV for the treatment of patients with advanced or metastatic (stage IV) pancreatic cancer who have been previously treated with gemcitabine based therapy (any line), including gemcitabine in non-adjuvant/adjuvant/locally advanced patients who are now diagnosed with metastatic disease.

5.2 ERG critique of the company's literature review

The ERG is satisfied with the company's search strategy and is confident that there are no cost effectiveness studies that fully meet the company's inclusion criteria. The databases searched and search terms used appear to be reasonable.

The company also reports the methods and results for searches carried out to identify HRQoL data relevant to the decision problem. Further detail on these searches are given in Section 5.3.5 of this ERG report, and in the CS (Section 5.4.3 and Appendix 9). The ERG considers these details to be helpful.

5.3 Summary of the company's submitted economic evaluation

The company has developed a de novo economic model to allow the comparison of three treatment regimens: nal-iri+5-FU/LV, oxaliplatin+5-FU/LV and 5-FU/LV monotherapy.

The company model is a partitioned survival model which comprises four mutually exclusive health states: pre-progression on treatment, pre-progression off treatment, post-progression treatment (including patients receiving second-line therapy and those receiving palliative care) and death. All patients enter the model in the pre-progression on treatment health state. At the beginning of each time period patients can either remain in the same health state or progress to a worse health state. For example, patients in the pre-progression on treatment health state can move to the pre-progression off treatment health state, the post-progression treatment state or the death state, whilst patients in the post-progression treatment state can only move to the death state. A schematic of the company model is reproduced in Figure 2. The ERG has added two blue arrows to Figure 2 as, in the company model, patients may move directly from either of the pre-progression treatment states (pre-progression on treatment and pre-progression off treatment) to the death state.

Estimates of OS, PFS and TTF for patients treated with nal-iri+5-FU/LV and 5-FU/LV are based on K-M data from the NAPOLI-1 trial. Estimates of OS, PFS and TTF for patients treated with oxaliplatin+5-FU/LV are based on data from an ITC combined with various assumptions. The proportion of patients in the pre-progression on treatment health state is estimated as the difference between PFS and TTF. The proportion of patients in the post-progression treatment state is estimated as the difference between OS and PFS.

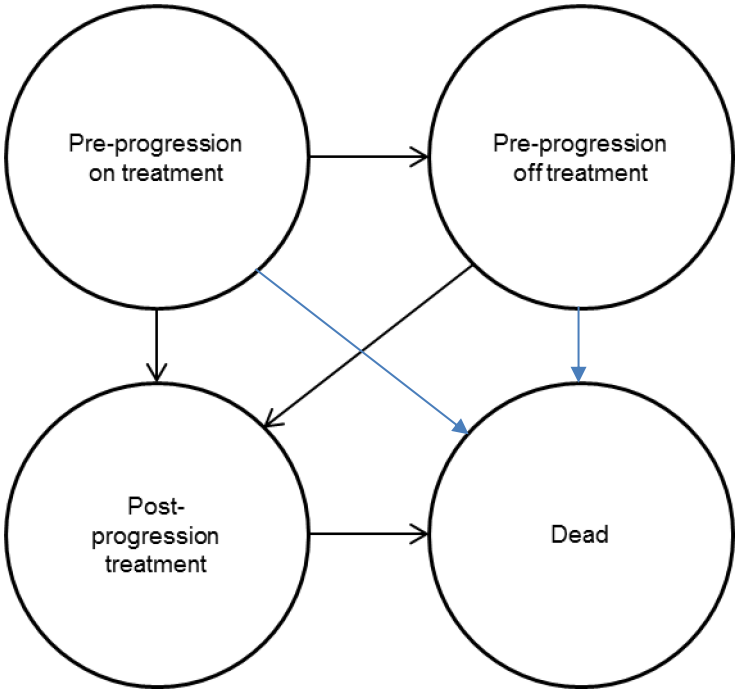

Figure 2 Company model structure

Source: CS, adapted from Figure 8 (Blue lines added by the ERG)

5.3.1 Population

The population reflected in the company model is adult patients with metastatic adenocarcinoma of the pancreas who have progressed following gemcitabine based therapy, as per the NICE scope and the NAPOLI-1 trial.

Based on the results of a study of the average body surface area (BSA) of adult cancer patients in the UK,[39] the company has assumed that population BSA is 1.79m^2. The company notes that this BSA value is similar to the BSA of the NAPOLI-1 trial ITT population (1.75m^2). Age and sex are not variables in the model.

5.3.2 Interventions and comparators

Pre-progression treatment

The company model allows the cost effectiveness of nal-iri+5-FU/LV to be compared with oxaliplatin+5-FU/LV (NHS standard of care) and 5-FU/LV (a comparator in the NAPOLI-1 trial). Dosing schedules and dosing levels differ between the intervention and each comparator. Dosing schedules used in the company model are displayed in Table 30.

Table 30 Dosing schedules

Treatment	Nal-iri+5-FU/LV (Intervention)	Oxaliplatin+5-FU/LV (NHS standard of care)	5-FU/LV (NAPOLI-1 trial comparator)
Nal-iri dose	80mg/m^2	--	--
Oxaliplatin dose	--	85mg/m^2	--
LV dose	400mg/m^2	200mg/m^2	200mg/m^2
5-FU dose	2400mg/m^2	1000mg/m^2	2000mg/m^2
5-FU delivery time	46hrs	46hrs	24hrs
Dosing frequency	Every 2 weeks	Every 2 weeks	Days 1, 8, 15 and 22 followed by 2 weeks rest in a 6 week cycle

-- not applicable
Source: CS, p123

Post-progression treatment

Based on the experience of patients included in the NAPOLI-1 trial, the company has assumed that 38% of patients receiving treatment with nal-iri+5-FU/LV and 31% of patients receiving treatment with 5-FU/LV monotherapy receive anti-cancer treatment post-progression. The company also assumes that the proportion of patients receiving oxaliplatin+5-FU/LV who go on to receive anti-cancer treatment post-progression is the same as the estimate used for the nal-iri+5-FU/LV cohort (38%). The company does not provide details of the post-progression treatments. It is not clear to the ERG whether these proportions relate to all patients or only those whose progression event was not fatal. The ERG also notes that within the company's clarification response figures from the NAPOLI trial show that the proportions of patients in the nal-iri+5-FU/LV and 5-FU/LV arms who received anti-cancer treatment post-progression were 35.9% and 42.0% in the respectively.

5.3.3 Perspective, time horizon and discounting

The economic evaluation is undertaken from the perspective of the NHS. The time horizon is set at 10 years and both costs and outcomes are discounted at a rate of 3.5% per annum.

5.3.4 Treatment effectiveness and extrapolation

Nal-iri+5-FU/LV and 5-FU/LV

The primary data source for the economic model was patient-level data from the final data cut of the NAPOLI-1 trial (March 2016). At this point all patients were dead. The company modelled survival and TTF using parametric distributions fitted to K-M data taken from the NAPOLI-1 trial.

The company compared six standard parametric models (exponential, Weibull, Gompertz, log-logistic, log-normal and gamma). The most appropriate distribution was chosen based on how well the distribution fitted K-M data from the NAPOLI-1 trial (assessed using Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC] statistics) and the

clinical and biological plausibility of the distribution. This approach resulted in log-normal distributions being selected to model OS, PFS and TTF in the base case. Log-logistic distributions were used to model these parameters in a scenario analysis. Key survival and TTF parameter values from the NAPOLI-1 trial and the company model are displayed in Table 31. The NAPOLI-1 trial OS and PFS K-M data used in the company model are shown in Figure 3 and Figure 4 respectively.

Table 31 Key NAPOLI-1 trial and model survival and time to treatment failure parameter values

	Figures used in company model		Figures in CS, where different from company model	
Parameter values	**Nal-iri+5-FU/LV**	**5-FU/LV**	**Nal-iri+5-FU/LV**	**5-FU/LV**
PFS				
NAPOLI-1 trial median, months	3.1	1.5	-	-
Company model median, months	3.49*	2.09	3.47	-
Company model mean, months	5.47*	2.81	5.45	-
OS				
NAPOLI-1 trial median, months	6.2	4.2	-	-
Company model median, months	6.75*	4.66*	6.24	4.67
Company model mean, months	10.20*	7.69*	10.18	7.66
TTF				
NAPOLI-1 trial median, months	1.6	0.76	-	-
Company model median, months	1.7	1.10	-	-
Company model mean, months	4.6	2.0	-	-

CS=company submission; OS=overall survival; PFS=progression-free survival; TTF=time to treatment failure
Source: CS, Table 37 and company model

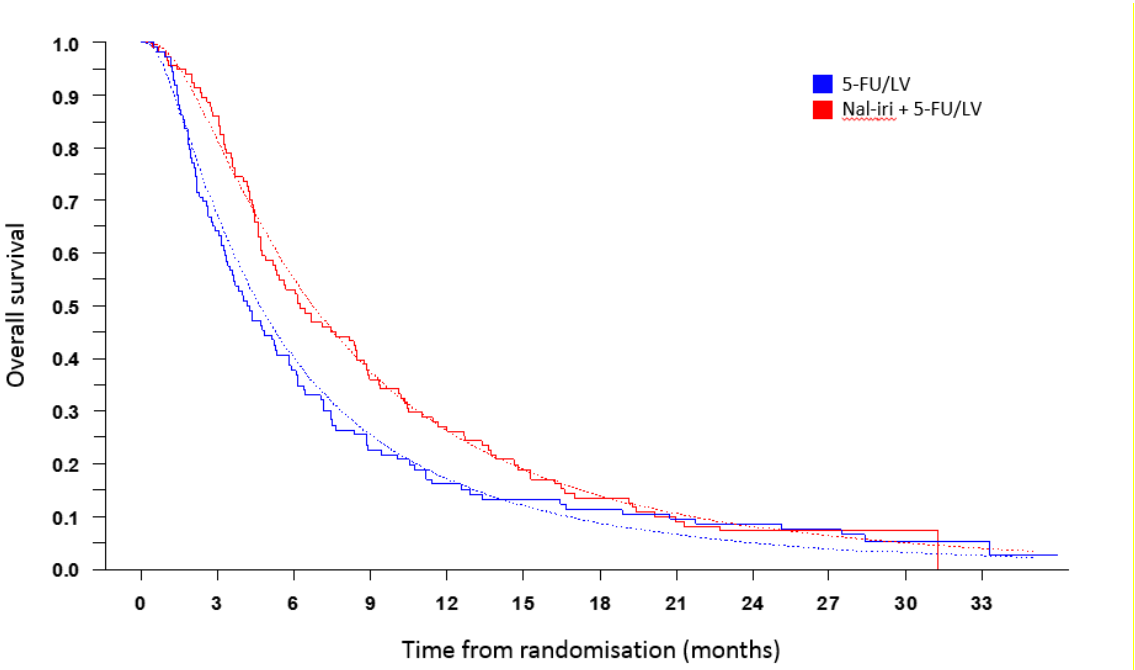

Figure 3 Base case (log-normal) model fit to overall survival

Source: CS, Figure 10

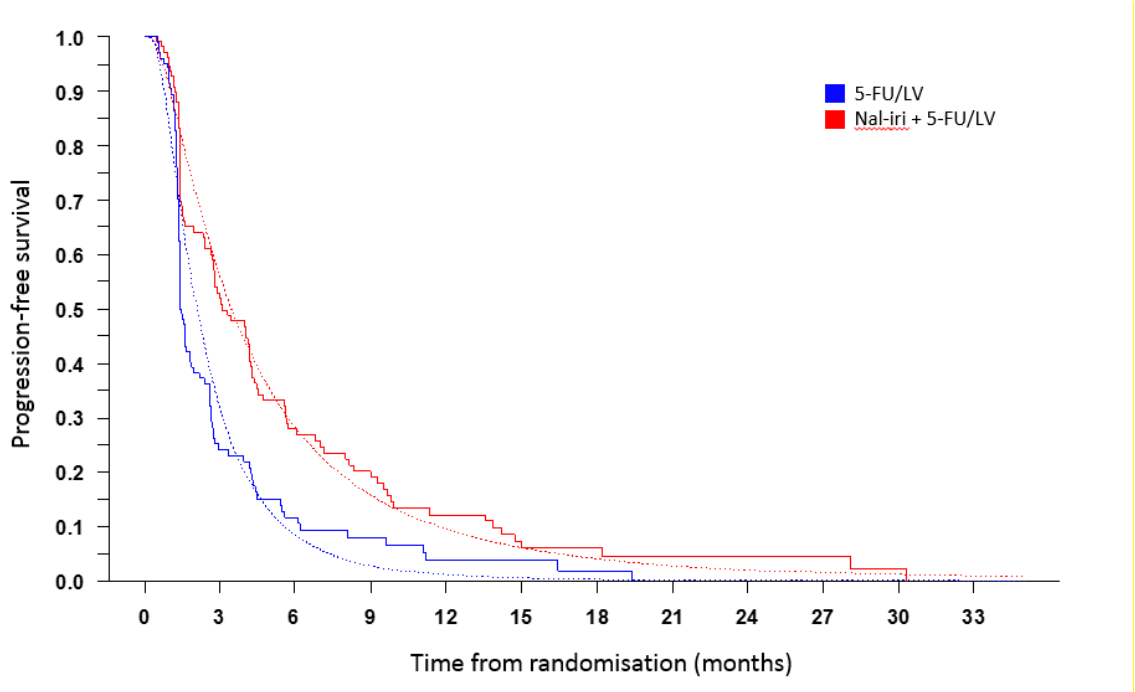

Figure 4 Base case (log-normal) model fit to progression-free survival

Source: CS, Figure 11

Oxaliplatin+5-FU/LV

The company performed an ITC (using the Bucher adjusted ITC method[35]) to generate estimates for the effectiveness of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV using data from the CONKO-003 and PANCREOX clinical trials. The resultant PFS and OS HRs were used to adjust the 5-FU/LV base case PFS and OS models to generate survival estimates for patients treated with oxaliplatin+5-FU/LV.

The company notes the limitations of two key assumptions that underpin the ITC methodology. First, the survival estimates for oxaliplatin+5-FU/LV from the ITC rely on the assumption that the dosing regimens for oxaliplatin+5-FU/LV used in the CONKO-003 and PANCREOX trials (OFF and FOLFOX6, respectively) are equivalent. Second, the application of survival estimates from the ITC relies on the assumption of PH between the nal-iri+5-FU/LV and 5-FU/LV arms of the NAPOLI-1 trial, which the company states do not hold for OS.

A critique of the ITC may be found in Section 4.3 of this ERG report.

5.3.5 Health related quality of life

The cancer-specific EORTC-QLQ-C30 questionnaire was used during the NAPOLI-1 trial to collect HRQoL data. The company states that they did not map between EORTIC-QLC-30 and EuroQol-5 dimension (EQ-5D) utility values because:

- a substantial amount of HRQoL data were missing, with the majority of the missing data being due to discontinuation of treatment because of disease progression, adverse events or death (i.e. not random)
- although one potential mapping algorithm was identified,[40] this was an ASCO abstract and no algorithm was available.

The company conducted a systematic review to identify HRQoL studies relevant to the decision problem. Studies reporting health state utility values relating to patients with metastatic pancreatic cancer were considered eligible for inclusion. Full details of the company's search are included in Appendix 9 of the CS. Six studies met the inclusion criteria for the review.

Utility values from a US study, adjusted first to reflect the values of the UK population and then further adjusted to include disutility associated with AEs, are used in the company model. The US utility values, adjusted to reflect the values of the UK population but without AE associated disutility adjustments, have previously been used by the ERG[41] during the

NICE appraisal of nab-paclitaxel in combination with gemcitabine for previously untreated metastatic pancreatic cancer (TA360).[13]

A summary of the utility values employed in the model is included in Table 32.

Table 32 Summary of utility values for cost effectiveness analysis

	Utility value	95% CI	Reference	Justification
5-FU/LV				
Baseline utility value				
Pre-progression	0.742	NR	TA360 ERG report[41]	Utility data from NAPOLI-1 trial could not be used
Post-progression	0.671*	NR		
Nal-iri+5-FU/LV				
Baseline utility value				
Pre-progression	0.742	NR	TA360 ERG report[41]*	Utility data from NAPOLI-1 trial could not be used
Post-progression	0.671*	NR		
Oxaliplatin+5-FU/LV				
Baseline utility value				
Pre-progression	0.742	NR	TA360 ERG report[41]	Assumed to be equivalent to nal-iri + 5-FU/LV
Post-progression	0.671*	NR		
Adverse events (utility decrements)				
Abdominal pain	–0.069	-0.093 to -0.045†	Doyle, 2008[42]	
Anaemia	–0.204	-0.156 to -0.252	-	Assumed equivalent to fatigue
Diarrhoea	–0.204	-0.156 to -0.252	-	
Fatigue	–0.204	-0.156 to -0.252	Swinburn, 2010[43]	
Nausea	–0.048	-0.079 to -0.016	Nafees, 2008[44]	
Neutropenia	–0.090	-0.122 to -0.058	Nafees, 2008[44]	
Vomiting	–0.048	–0.079 to –0.016	-	Assumed equivalent to nausea

AE=adverse event; ERG=Evidence Review Group; NR=not reported
*Indicates value amended during clarification process (0.672 in original submission)
Source: CS, Table 42

5.3.6 Resources and costs

Drug costs

Table 33 shows the unit costs of drugs included in the company model.

Table 33 Drug unit costs

Items	Vial size	Cost per vial	Cost per unit	Reference
Nal-iri	50mg	[redacted]	[redacted]	CS
5-FU bolus injection	500mg	£12.80	£0.0128*	BNF 2016[45]
5-FU infusion	500mg	£64.00	£0.0128*	
LV	50mg	£100.00	£0.375	
Oxaliplatin	50mg	£311.00	£3.11*	

BNF=British National Formulary
*Indicates values that differ between the CS and the company model. Where there is a discrepancy, values from the company model are presented
Source: CS, Table 45 and company model

The company calculates average drug costs from the average number of vials used per patient. The average number of vials used for each drug is based on the probability of needing a given number of vials based on a normal distribution of the dose per patient. The average number of vials used also takes into account the recommended dose per m^2 and assumes that 5-FU comes in 500mg vials and all other drugs come in 50mg vials. The average dose per patient is calculated based on mean BSA and the recommended dose of the drug, and is then adjusted using a dose intensity multiplier to allow treatment costs to be adjusted for missed and reduced doses. The values of these multipliers are provided in Table 34.

Table 34 Mean dose intensity multipliers used in the company model

Treatment	Mean dose intensity multiplier	Reference
Nal-iri+5-FU/LV	85%	NAPOLI-1 trial
Oxaliplating+5-FU/LV	85%	Assumption
5-FU-LV	95%	NAPOLI-1 trial

Source: Company model

Administration costs

The company has used NHS Reference Costs as the source of administration costs for each treatment. The first drug administered in any regimen is costed as simple parental chemotherapy (£239.12) and subsequent drugs are assumed to require 30 minutes of nurse time (£18.00) to remove the initial infusion and to set up the next infusion. Because of the long infusion time associated with 5-FU treatment, an additional cost of £97.14 (non-consultant outpatient attendance, medical oncology) is applied to account for resource use associated with the patient's return to hospital to have the infusion pump removed as an outpatient. The costs of administering each treatment are displayed in Table 35.

Table 35 Administration costs for nal-iri+5-FU/LV, 5-FU/LV and oxaliplatin+5-FU/LV

	Nal-iri+5-FU/LV			Oxaliplatin+5-FU/LV			5-FU/LV	
	Nal-iri	5-FU	LV	Oxaliplatin	5-FU	LV	5-FU	LV
Administration cost	£239.12	£115.14	£18.00	£239.12	£115.14	£18.00	£115.14	£239.12
Total cost per treatment	£372.26			£372.26			£354.26	
Cost per week	£186.13			£186.13			£236.17	

Source: Company model

Treatment-related monitoring costs

The company has assumed that patients will be monitored until the termination of active anti-cancer treatments. Monitoring costs are split into two: initial monitoring costs prior to the start of therapy, and monitoring costs during the treatment period. Initial monitoring costs include laboratory tests in preparation for the initiation of treatment and are only applied to the first cycle of the model. After the initiation of treatment, patients are monitored with follow-up visits and laboratory tests for as long as they remain on active treatments. Treatment-related monitoring costs used in the model are shown in Table 36 and Table 37.

Table 36 Initial monitoring and laboratory test costs

Visit and tests	Unit cost	Reference	Proportion of patients	Cost per week
Outpatient visit (consultant)	£170.85	NHS Reference Costs 2014-15[46]	100%	£170.85
CT scan	£108.71		100%	£108.71
Radiographic/MRI scan	£181.76		10%	£18.18
Full blood count	£3.01		100%	£3.01
Liver function test	£6.89		100%	£6.89
Ultrasound	£53.74		5%	£2.69

CT=computed tomography; MRI=magnetic resonance imaging
Source: CS, Table 48

Table 37 Monitoring costs during treatment

Visit and test	Unit costs	Reference	Number	Frequency	Proportion of patients	Cost per week
Community visit (nurse)	£44.00	Curtis 2015[47]	1	Every 4 weeks	60%*	£6.60
Outpatient visit (consultant)	£170.85	NHS Reference Costs 2014-15[46]	1	Every 4 weeks	100%	£42.71
Outpatient visit (non-consultant)	£97.14		1	Every 4 weeks	50%	£12.14
CT scan	£108.71		1	Every 12 weeks	100%	£9.06
Full blood count	£3.01		3	Every 4 weeks	100%	£2.26
Liver function test	£6.89		3	Every 4 weeks	100%	£5.17
Tumour Marker CA19-9 test	£1.38		6	Every 4 weeks	100%**	£2.07

CT=computed tomography
* 50% in CS but 60% used in model
** 5% in CS but 100% used in model
Source: CS, Table 49 and company model

Adverse event costs

The company has included costs associated with grade 3+ TEAEs reported by ≥5% of patients in the model. Costs of managing each AE are listed in Table 38. The expected number of each AE per patient for each treatment was estimated based on data from the NAPOLI-1 trial, with costs associated with AEs for patients treated with oxaliplatin+5-FU/LV assumed to be equal to those for patients treated with nal-iri+5-FU/LV.

Table 38 Summary of weekly costs included in the cost effectiveness model

Adverse events	Value	HRG code	Reference
Anaemia	£528.15	SA04L	NHS Reference Costs 2014-15[46]
Neutropenia	£127.70	XD25Z	
Abdominal pain	£387.25	FZ90A – FZ90B	
Diarrhoea	£319.34	FZ49D - FZ49H	
Nausea	£319.34	NA	Assumed to be the same as diarrhoea
Vomiting	£319.34	NA	
Fatigue	£44.00	NA	1 nurse visit per day for the duration of the adverse event[47]

HRG=Healthcare Resource Group; NA=not applicable
Source: CS, Table 50

Post-progression treatment costs

Patients in the NAPOLI-1 trial were eligible to receive other anti-cancer therapies following progression. However, the company notes that no details about the costs of these subsequent therapies were collected during that trial. The company has assumed that the average weekly cost of post-progression treatment is equal to the weekly drug cost for nal-iri+5-FU/LV ([redacted]). Patients who receive anti-cancer therapy post-progression continue

to receive treatment until death. The weekly costs for post-progression treatment are summarised in Table 39.

Table 39 Costs of post-progression treatment

	Nal-iri+ 5-FU/LV	Oxaliplatin+ 5-FU/LV	5-FU/LV	Reference
Cost of post-progression treatments	[redacted]	[redacted]	[redacted]	Assumed equal to nal-iri
Percent of patients**	31%†	Assumed equal to nal-iri+5-FU/LV, i.e. 31%	38%†	NAPOLI-1 trial
Average cost per week	[redacted]	[redacted]	[redacted]	

*This is the figure used in the model; however, the figure reported in the CS is [redacted]
**It is not clear to the ERG whether these proportions relate to all patients or only those whose progression event was not fatal.
†These are the figures used in the model and reported in the CS; however, the figures quoted in the clarification response are 35.9% and 42.0% for the nal-iri+5-FU/LV and 5-FU/LV arms respectively
Source: CS, Table 53, company model and clarification response

Palliative- and terminal-care costs

The company assumes that patients who do not go on to receive anti-cancer therapy post-progression receive palliative care, which amounts to one home care visit by a nurse every week until death. The percentage of patients who receive palliative care in the model is based on the percentage of patients who did not switch to another anti-cancer therapy following disease progression in the NAPOLI-1 trial: 69% in the nal-iri+5-FU/LV arm and 62% in the 5-FU/LV arm. The company assumes that the percentage of patients receiving oxaliplatin+5-FU/LV who receive palliative care is equal to the percentage of patients treated with nal-iri+5-FU/LV who receive palliative care.

In line with the model submitted as part of the NICE TA360[13] appraisal, the company assumes that terminal care is provided to patients in the 4 weeks prior death. The company accounts for terminal care costs in the model by assuming that, 4 weeks before death, 50% of patients receive more frequent home visits by a nurse and 50% of patients are moved to hospice care. Terminal care costs are included in addition to ongoing palliative care costs.

The palliative- and terminal-care costs included in the company model are provided in Table 40 and Table 41 respectively.

Table 40 Palliative care costs

Item	NAl-iri+ 5-FU/LV	Oxaliplatin+ 5-FU/LV	5-FU/LV	Reference
Nurse home care visit per week	1			Advisory board
Costs per nurse home care visit	£44.00			NHS Reference Costs 2014-15[46]
Percent of patients	69%†	Assumed equal to nal-iri+5-FU/LV	62%†	NAPOLI-1 trial*
Average cost per week	£30.36	£30.36	£27.28	

NHS=National Health Service.
*Percentages are for patients who did not switch to anti-cancer therapy following disease progression
†Indicates values that differ between the company clarification response and the company model. Where there is a discrepancy, values from the company model are presented
Source: CS, Table 51

Table 41 Terminal care costs incurred in the 4 weeks before death

Items	No.	Frequency	% of patients	Unit cost	Source	Cost per week
Nurse home care	3	Every week	50%	£44.00	Curtis 2015 [47]	£66.00
Hospice centre/ palliative care unit	7	Every week	50%	£103.01	NHS Reference Costs, 2014-15	£360.54
Total						£426.54

Source: CS, Table 52

5.3.7 Cost effectiveness results

Base case results

Base case incremental cost effectiveness results for treatment with nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV and versus 5-FU/LV are shown in Table 42. Pairwise cost effectiveness results for the comparison of treatment with nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV and of nal-iri+5-FU/LV versus 5-FU/LV are shown in Table 43 and Table 44 respectively.

In the base case, nal-iri+5-FU/LV generates 0.20 additional quality adjusted life years (QALYs) and 0.31 additional life years compared with oxaliplatin+5-FU/LV and, compared with 5-FU/LV, generates an additional 0.13 QALYs and an additional 0.21 life years. Patients treated with nal-iri+5-FU/LV-are estimated to have higher total lifetime costs than patients receiving either of the other two treatments. The incremental cost effectiveness ratio (ICER) for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV is £[redacted] per QALY gained and the ICER for the comparison of nal-iri+5-FU/LV versus 5-FU/LV is £[redacted] per QALY gained.

Table 42 Base case model results (incremental)

Technologies	Total		Incremental		ICER (Cost/QALY)
	Costs	QALYs	Costs	QALYs	
5-FU/LV	£13,338.32	0.4294			
Oxaliplatin+5-FU/LV	£13,974.83	0.3621	£636.51	-0.0673	[redacted]
Nal-iri+5-FU/LV	[redacted]	0.5635	[redacted]	0.1341	[redacted]

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
Source: CS, Table 55 (costs and QALYs) and ERG calculations (incremental results)

Table 43 Base case cost effectiveness results (nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV)

Technologies	Total		Incremental		ICER (Cost/QALY)
	Costs	QALYs	Costs	QALYs	
Nal-iri+5-FU/LV	[redacted]	0.5635	-	-	-
Oxaliplatin+5-FU/LV	£13,974.83	0.3621	[redacted]	0.2013	[redacted]

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
Source: CS, Table 55

Table 44 Base case cost effectiveness results (nal-iri+5-FU/LV versus 5-FU/LV)

Technologies	Total		Incremental		ICER (Cost/QALY)
	Costs	QALYs	Costs	QALYs	
Nal-iri+5-FU/LV	[redacted]	0.5635	-	-	-
5-FU/LV	£13,338.32	0.4294	[redacted]	0.1341	[redacted]

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
Source: CS, Table 55

Disaggregated cost estimates for treatment with nal-iri+5-FU/LV, oxaliplatin+5-FU/LV and 5-FU are shown in Table 45 and Table 46. Disaggregated QALY estimates for treatment with nal-iri+5-FU/LV, oxaliplatin+5-FU/LV and 5-FU/LV are shown in Table 47 and Table 48.

Table 45 Disaggregated cost estimates (nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV)

Health state	Nal-iri+ 5-FU/LV	Oxaliplatin+ 5-FU/LV	Increment	Absolute increment	% absolute increment
Drug	[redacted]	£4,450*	[redacted]	[redacted]	[redacted]
Admin	£3,174	£2,655	£518	£518	[redacted]
AE	£242	£202	£39	£39	[redacted]
Monitoring	£1,675	£1,452	£223	£223	[redacted]
Palliative	£2,492	£2,098	£394	£394	[redacted]
Pre-progression	£25,507	£6,407	£14,621	£14,621	[redacted]
Post-progression	£5,578	£3,117	£2,461	£2,461	[redacted]
Total	[redacted]	£19,975*	[redacted]	[redacted]	100%

AE=adverse event
*Indicates values that differ between the CS and the company model. Where there is a discrepancy, values from the company model are presented
Source: CS, Table 60 and company model

Table 46 Disaggregated cost estimates (nal-iri+5-FU/LV versus 5-FU/LV)

Health state	Nal-iri+ 5-FU/LV	5-FU/LV	Increment	Absolute increment	% absolute increment
Drug	[redacted]	£971	[redacted]	[redacted]	[redacted]
Admin	£3,174	£1,874	£1,300	£1,300	[redacted]
AE	£242	£74	£168	£168	[redacted]
Monitoring	£1,675	£945	£730	£730	[redacted]
Palliative	£2,492	£2,372	£120	£120	[redacted]
Pre-progression	£25,507	£6,236	£18,885	£18,885	[redacted]
Post-progression	£5,578	£7,103	-£1,525	£1,525	[redacted]
Total	[redacted]	£13,338	[redacted]	[redacted]	100%

AE=adverse event
Source: CS, Table 59

Table 47 Summary of QALY gain by health state for nal-iri+5-FU/LV versus 5-FU/LV

Health state	Nal-iri+ 5-FU/LV	5-FU/LV	Increment	Absolute increment	% total absolute increment
Pre-progression	0.3279	0.1724	0.1555	0.1555	116%
Post-progression	0.2355	0.2569	-0.0214	0.0214	-16%
Total	0.5635	0.4294	0.1341	0.1341	100%

QALY=quality adjusted life year
Source: Company model

Table 48 Summary of QALY gain by health state for nal-iri+5-FU/LV versus oxaliplatin+5 FU/LV

Health state	Nal-iri+ 5-FU/LV	Oxaliplatin+ 5-FU/LV	Increment	Absolute increment	% absolute increment
Pre-progression	0.3279	0.2305	0.0974	0.0974	48%
Post-progression	0.2355	0.1316	0.1039	0.1039	52%
Total	0.5635	0.3621	0.2013	0.2013	100%

QALY=quality adjusted life year.
Source: Company model

5.3.8 Sensitivity analyses

Deterministic sensitivity analysis

The company did not provide any deterministic sensitivity analyses for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV.

One-way sensitivity analyses were conducted for the comparison of nal-iri+5-FU/LV versus 5-FU/LV. The sensitivity analyses involved varying 44 cost, resource use and utility parameter values (see CS, Table 62). The base case ICER per QALY gained was most sensitive to varying the pre-progression utility values. The results were also sensitive to the cost of nal-iri and to mean BSA. All other variables had minimal impact on the size of the ICER per QALY gained. The tornado diagram in Figure 5 shows the ten parameters with the biggest impact on the ICER per QALY gained for the comparison of nal-iri+5-FU/LV versus 5-FU/LV.

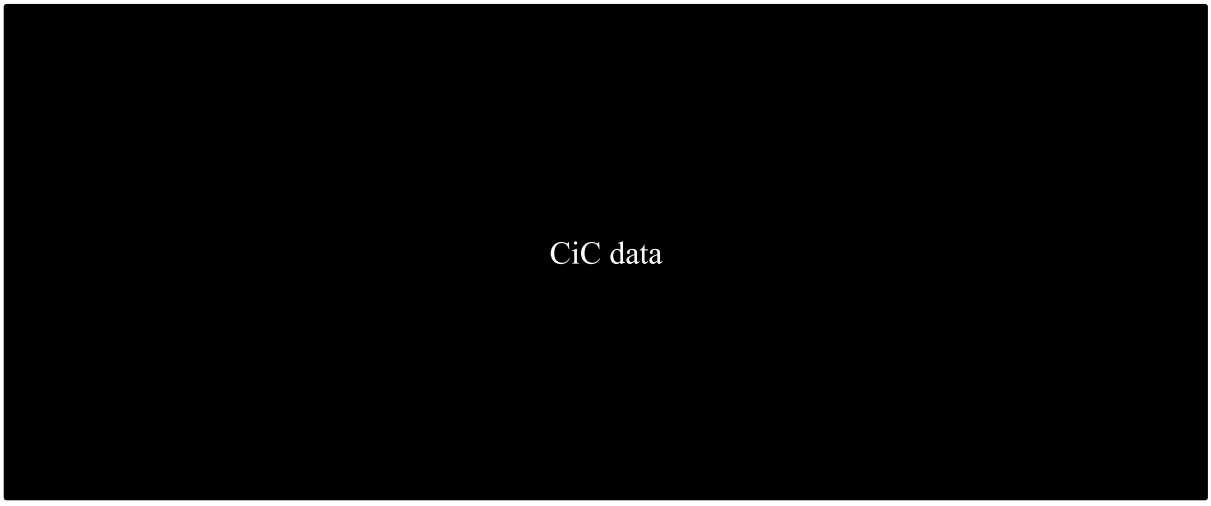

Figure 5 Tornado diagram of deterministic sensitivity analysis ICERs for the comparison of nal-iri+5-FU/LV versus 5-FU/LV

Admin=administer; BSA=body surface area; chemo=chemotherapy
Source: CS, Figure 21

Scenario analyses

Three scenario analyses were undertaken by the company, namely:

1. using data from the February 2014 data cut from the NAPOLI-1 trial instead of from the March 2016 data cut
2. omitting utility decrements associated with AEs and
3. using a log-logistic instead of log-normal distribution for PFS, OS and TTF for nal-iri+5-FU/LV versus 5-FU/LV.

The results of these scenario analyses are shown in Table 49.

Table 49 Scenario analyses results

Scenario	ICER per QALY gained	
	Nal-iri+5-FU/LV versus 5-FU/LV	Nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV
Base case	[redacted]	[redacted]
February 2014 data cut from NAPOLI-1 trial using log-normal distribution	[redacted]	[redacted]
AE utility decrements omitted	[redacted]	[redacted]
Log-logistic distribution for PFS, OS and TTF for nal-iri+5-FU/LV versus 5-FU/LV	[redacted]	–

AE=adverse event; ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year; TTF=time to treatment failure
*Indicates values that differ between the CS and the company model. Where there is a discrepancy, values from the company model are presented
Source: CS, Table 63 and company model

Probabilistic Sensitivity Analysis

The company undertook probabilistic sensitivity analyses (PSA) to derive the mean ICERs per QALY gained for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV and for nal-iri+5-FU/LV versus 5-FU/LV. The PSAs were run for 1000 iterations. The ERG has recalculated these ICERs following identification of a calculation error. The company and ERG results are shown in Table 50.

The probabilistic ICER for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV is £85,525 per QALY gained, which is comparable to the deterministic ICER per QALY gained (Table 50). At a cost effectiveness threshold of £50,000 per QALY gained, treatment with nal-iri+5-FU/LV has a 0% probability of being cost effective compared with treatment with oxaliplatin+5-FU/LV. The cost effectiveness plane and cost effectiveness acceptability curve (CEAC) for this comparison are shown in Figure 6 and Figure 7 respectively.

Table 50 Deterministic and probabilistic ICER results

Treatment	Incremental costs	Incremental QALYs	ICER per QALY gained	
			CS	ERG calculation*
Deterministic results				
Nal-iri+5-FU/LV				
Oxaliplatin+5-FU/LV	[redacted]	0.2013	[redacted]	-
5-FU/LV	[redacted]	0.1341	[redacted]	-
Probabilistic sensitivity analysis results				
Nal-iri+5-FU/LV				
Oxaliplatin+5-FU/LV, model (CS)	[redacted]	0.1348	[redacted]	[redacted]
5-FU/LV, model (CS)	[redacted]	0.2035	[redacted]	[redacted]

CS=company submission; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
*ERG re estimated probabilistic ICERs as the company's calculations were incorrect
Source: CS and company model

Figure 6 Cost effectiveness plane for nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV

QALY=quality adjusted life year
Source: CS, Figure 19

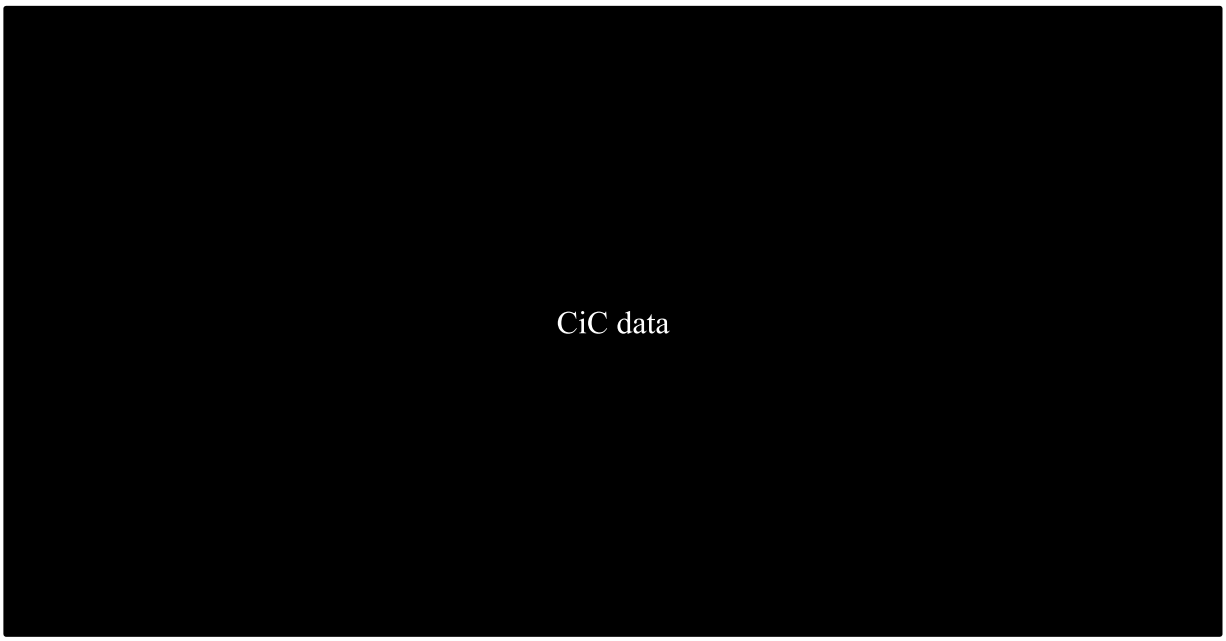

Figure 7 Cost effectiveness acceptability curve for nal-iri+5-FU/LV versus oxaliplatin+5 FU/LV

QALY=quality adjusted life year
Source: CS, Figure 20

The probabilistic ICER for the comparison of nal-iri+5-FU/LV versus 5-FU/LV is £[redacted] per QALY gained, which is also comparable to the deterministic ICER per QALY gained (Table 50), but is more variable than the probabilistic ICER per QALY gained for the comparison of

nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV. This is because the company assumes that many of the parameters in the estimate of the ICER per QALY gained for oxaliplatin+5-FU/LV are equal to those for nal-iri+5-FU/LV, which reduces the uncertainty in the probabilistic analysis. There are few assumptions of parameter equality in the calculation of the probabilistic ICER per QALY gained for nal-iri+5-FU/LV versus 5-FU/LV, which means there is likely to be more uncertainty in this PSA ICER per QALY gained than there is in the PSA ICER per QALY gained for nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV. At a cost effectiveness threshold of £50,000 per QALY gained, treatment with nal-iri+5-FU/LV has a [redacted]% probability of being cost effective compared with treatment with 5-FU/LV. The cost effectiveness plane and CEAC for this comparison are shown in Figure 8 and Figure 9 respectively.

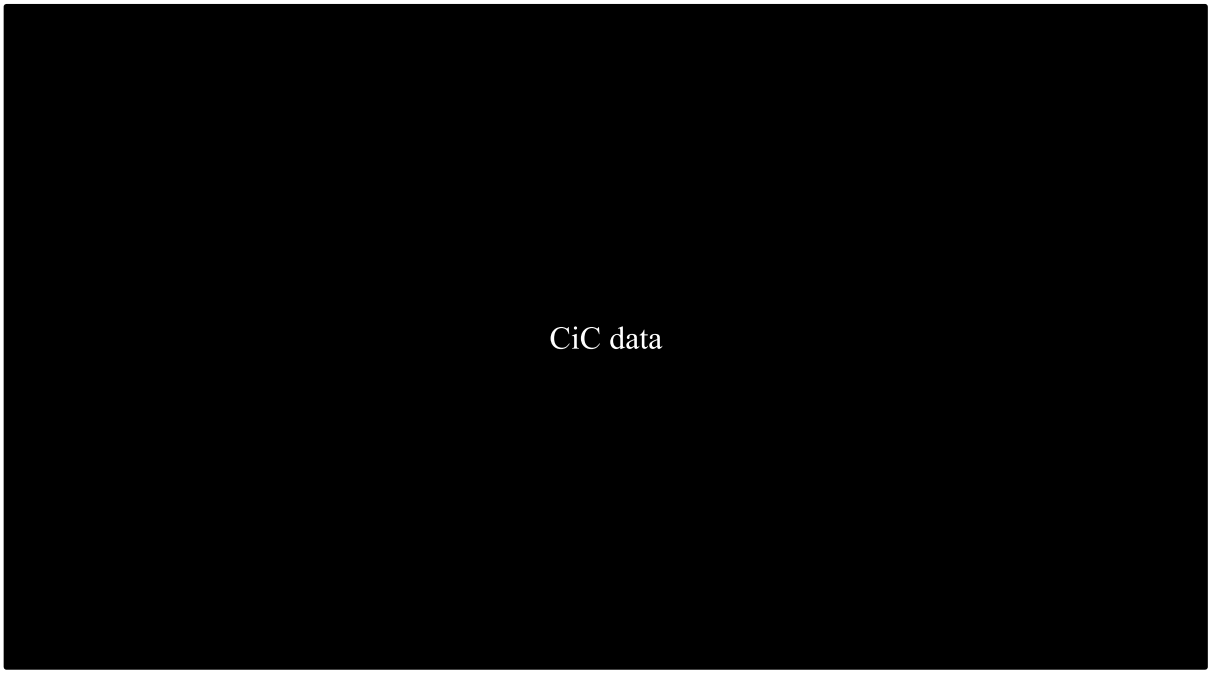

Figure 8 Cost effectiveness plane for nal-iri+5-FU/LV versus 5-FU/LV

QALY=quality adjusted life year
Source: CS, Figure 17

Figure 9 Cost effectiveness acceptability curve for nal-iri+5-FU/LV versus 5-FU/LV

QALY=quality adjusted life year
Source: CS, Figure 18

5.3.9 Model validation and face validity check

The company states that their model was validated through a multi-step process to verify the structure and underlying modelling and economic assumptions, which was followed by verification of all numerical data included in the model and mark-up of the reference publication. The model development team was supported by a quality control team that was not involved in model development. A model verification checklist was followed.

5.4 Completed model checklists

5.4.1 NICE reference case checklist

Table 51 NICE Reference case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Partial -amended to specify the combination of nal-iri with 5-FU in line with the revised indication in the SmPC
Comparator(s)	As listed in the scope developed by NICE	Partial - oxaliplatin in combination with capecitabine was excluded due to lack of published data. Fluoropyrimidine (5-fluorouracil) was included in combination with leucovorin (5-FU/LV). FOLFOX6 was included as oxaliplatin+5-FU/LV
Perspective costs	NHS and PSS	Partial - the model only includes NHS costs. Personal Social Service costs have not been considered
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Partial - patient related direct health effects are considered. No impact on carers has been considered in the model
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – 10 year time horizon
Synthesis of evidence on outcomes	Based on systematic review	Survival and time on treatment data associated with treatment with nal-iri+5-FU/LV with 5-FU/LV have been taken from the NAPOLI-1 trial The company carried out a systematic review to identify evidence to use in an ITC to allow a comparison of effectiveness between treatment with nal-iri+5-FU versus oxaliplatin+5-FU/LV. However, results from the company's ITC were considered unreliable (by both the company and the ERG)
Outcome measure	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects are expressed in QALYs
Health states for QALY	Reported directly by patients and/or carers	The company derived utility estimates using figures published in multiple sources
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes - NHS costs, valued at relevant prices, have been used. PSS costs are not included in the model
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Yes - benefits and costs have been discounted at the 3.5% rate
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes - all QALYs estimated by the economic model have the same weight

ERG=Evidence Review Group; EQ-5D=EuroQol-5 dimension; HRQoL=Health related quality of life; ITC=indirect treatment comparison; NICE=National Institute for Health and Care Excellence; PSS=personal social services QALY=quality adjusted life year; SmPC=summary of product characteristics;

5.4.2 Drummond checklist

Table 52 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	-
Was a comprehensive description of the competing alternatives given?	Yes	-
Was the effectiveness of the programme or services established?	Partial	Appropriate data available for nal-iri+5FU/LV and 5-FU/LV. Comparative effectiveness of nal-iri+5-FU/LV and oxaliplatin+5-FU/LV was not established
Were all the important and relevant costs and consequences for each alternative identified?	Yes	Key costs and outcomes were identified
Were costs and consequences measured accurately in appropriate physical units?	Yes	-
Were the cost and consequences valued credibly?	Partially	The ERG considers that the company's survival projections lack clinical credibility for both comparators. In addition, some of the unit costs were incorrectly calculated
Were costs and consequences adjusted for differential timing?	Yes	Discount rate of 3.5% per annum
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	ICER calculated correctly
Was allowance made for uncertainty in the estimates of costs and consequences?	Partially	Deterministic, scenario and probabilistic sensitivity analyses were undertaken for the nal-iri+5-FU/LV versus 5-FU/LV comparison. However, only scenario and probabilistic sensitivity analysis were undertaken for the comparison with oxaliplatin+5-FU/LV
Did the presentation and discussion of study results include all issues of concern to users?	Yes	The results are presented and discussed in detail and an end of life treatment case has been proposed by the company

ERG=evidence review group; ICER=incremental cost effectiveness ratio

5.5 ERG critique of company model and exploratory and sensitivity analyses

5.5.1 Introduction

The company's de novo economic model is constructed according to conventional modelling practice. The ERG considers that this structure captures the treatment and progression pathway for patients with metastatic pancreatic cancer and that it is appropriate to use model outputs to inform cost effectiveness decision-making. On clinical advice, the ERG considers oxaliplatin+5-FU/LV to be the main comparator to nal-iri+5-FU/LV as this is the current standard of care in the NHS. However, the ERG also considers this comparison to be flawed as the clinical effectiveness data used by the company to estimate the effectiveness of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV are unreliable and thus any cost effectiveness results relating to this comparison should be viewed with caution. The ERG does not consider 5-FU/LV to be a relevant comparator.

Sections 5.5.2 to 5.5.6 of this ERG report include details of the ERG's main concerns relating to the submitted model, namely the use of parametric distributions to represent and project mature time-to-event data, the use of unreliable data to represent the effectiveness of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV, the choice of health state utility values and the methods employed to cost drugs. The ERG has addressed additional minor concerns in Section 5.5.7. The ERG's preferred approach to modelling these elements is also presented in the relevant sections. Unless otherwise stated, all of the data from the NAPOLI-1 trial that have been used by the ERG originate from the published paper,[6] the CS or from the company's clarification response.

5.5.2 Indirect treatment comparison: nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV

Due to the absence of direct head-to-head clinical trial data, the company performed an ITC to obtain an estimate of the clinical effectiveness of treatment with nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV; the latter is the current standard of care in the UK. Despite the company indicating that an ITC was not credible due to violation of PH assumptions and heterogeneity between trials, the company considered that results from the ITC were necessary to allow a comparison of cost effectiveness to be undertaken. The ERG considers the HRs used to facilitate the company's ITC are unreliable. A full critique of the company's ITC may be found in Section 4.2 and Appendices to this ERG report (Section 11.3). The ERG highlights the fact that the PH assumption is not compatible with log-normal parametric models since these are accelerated time failure (AFT) models and do not produce a single HR.[48] Furthermore, the ERG determined that a time ratio (TR) adjustment could not be

performed due to the AFT assumption also being violated when examining NAPOLI-1 trial data.

Results from crude analyses carried out by the ERG suggest that, overall, the PFS and OS outcomes for patients treated with oxaliplatin+5-FU/LV reported in published trials are similar in magnitude to the PFS and OS outcomes of patients who were treated with nal-iri+5-FU/LV in the NAPOLI-1 trial (see Section 4.7 of this ERG report for further details). To aid the decision-making process, the ERG has performed a number of sensitivity analyses exploring the effect of altering key model effectiveness outcomes for oxaliplatin+5-FU/LV (Section 6, Table 60). Total QALY gains were altered to determine the uncertainty surrounding the clinical effectiveness of oxaliplatin+5-FU/LV.

5.5.3 Time-to-event data

Projection of time-to-event data: nal-iri+5-FU/LV versus 5-FU/LV

To capture survival benefits over time, the company fitted separate parametric models to K-M data from the nal-iri+5-FU/LV and 5-FU/LV treatment arms of the NAPOLI-1 trial. The parametric models were used to estimate OS, PFS, post progression survival (PPS) and pre-progression on-treatment (time on treatment).

The primary purpose of curve fitting is to anticipate what is likely to happen to patients remaining on treatment or at risk subsequent to a data cut. However, in the NAPOLI-1 trial almost all the trial data are complete so that in only one instance is there any need to extrapolate beyond the reported data (involving a single patient still at risk at data cut-off). Thus there is little or no value in fitting parametric survival functions to these data, as the original trial observations must take precedence over any theoretical mathematical construct. Furthermore, the company has not provided any biological rationale or justification for their selection of log-normal distributions to project survival. Log-normal models are invariably problematic, generally leading to overestimates of survival due to their distinctively long tails. The ERG considers that the model should make maximum use of the best available clinical effectiveness evidence (i.e. the mature survival data from the NAPOLI-1 trial) rather than replacing these data with fitted parametric models which serve only to increase uncertainty by concealing the underlying disease dynamic. During the clarification process, the ERG requested K-M data for the nal-iri+5-FU/LV and 5-FU/LV treatment arms of the NAPOLI-1 trial. The ERG has replaced the company projections with complete trial K-M data to estimate OS, PFS and time on treatment for patients treated with nal-iri+5-FU/LV, and PFS and time on treatment for patients treated with 5-FU/LV (Figure 10 to Figure 13).

Progression-free survival

Comparison of the company's log-normal curves and the K-M data from the NAPOLI-1 trial for PFS are presented in Figure 10. The company's log-normal curve overstates the PFS in both the nal-iri+5-FU/LV and 5-FU/LV treatment arms for the first 4 months of PFS, and then understates PFS from 6 months onwards, especially in the comparator arm.

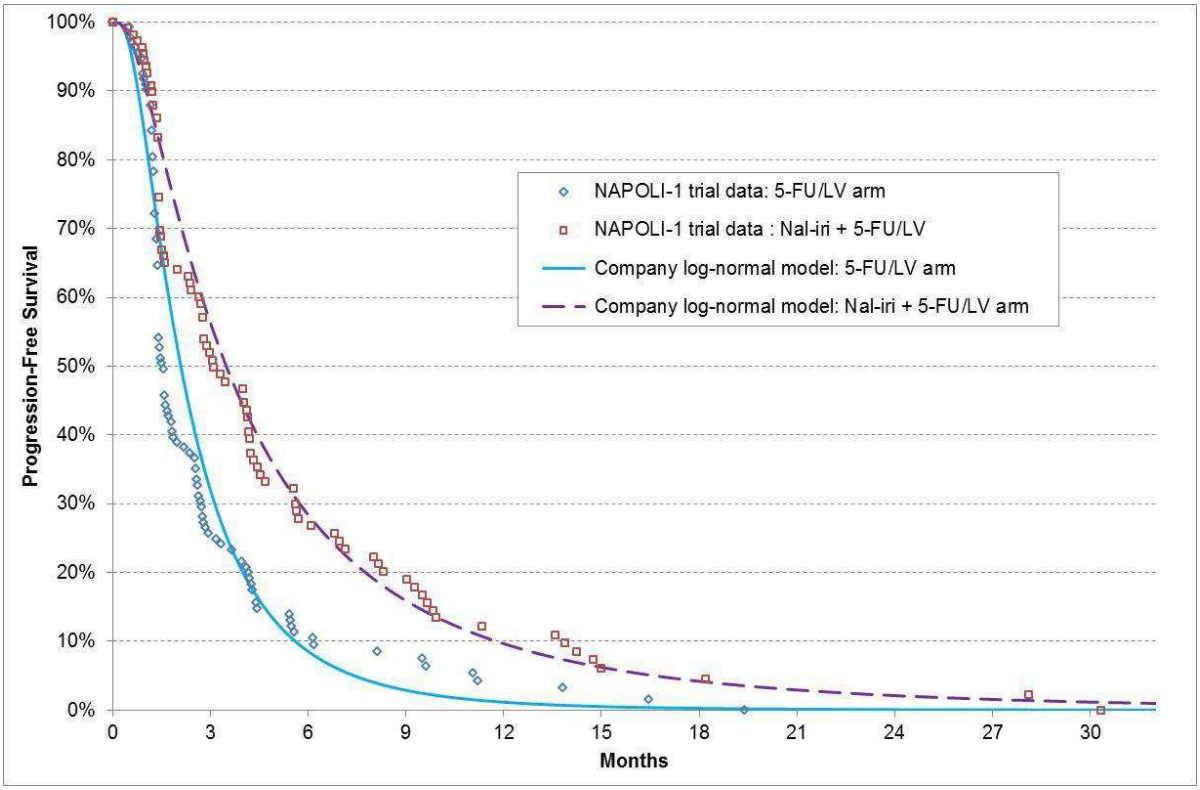

Figure 10 PFS company projections versus K-M data

The company model estimates a gain in mean PFS attributable to treatment with nal-iri+5-FU/LV of 2.657 months (5.472 versus 2.815) which is 4.8% greater than the accurate gain calculated by the K-M analysis of 2.535 months (5.677 versus 3.142).

Post-progression survival

The company model does not use PPS data from the NAPOLI-1 trial directly, but estimates PPS as the difference between estimated OS and PFS. This approach combines trial data which are complete with some which are not, and suggests that the mean PPS for nal-iri+5-FU/LV treated patients is 0.154 months less than that for patients in the comparator arm. In order to assess whether this model estimate of PPS gain is reliable, it is important to consider the PPS trial data directly (Figure 11).

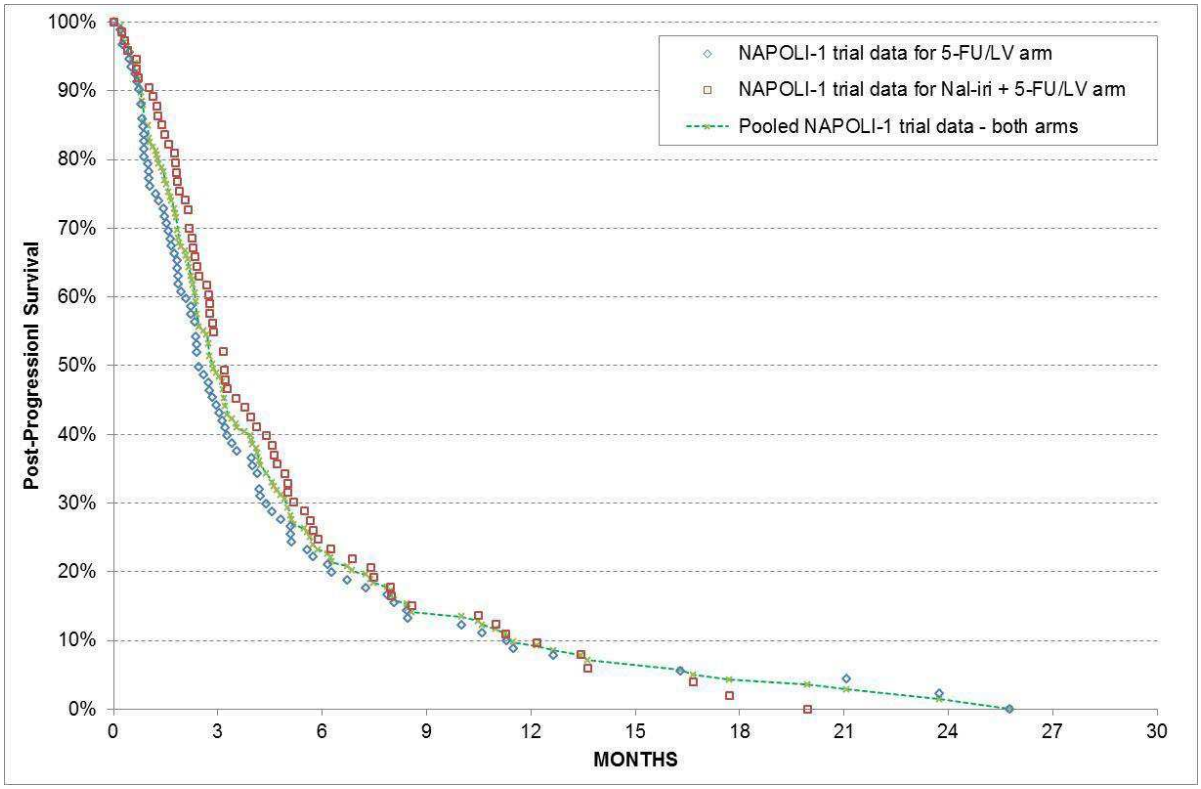

Figure 11 NAPOLI-1 PPS K-M data

The K-M analysis indicates that following disease progression there is no evidence that PPS differs by treatment arm (Log-rank test p=0.535). Therefore, the ERG has reanalysed the data, pooling patients from both arms of the NAPOLI-1 trial. Results from this analysis indicate that any patient surviving a progression event can expect a mean additional survival time of 4.897 months (the shape of the survival curve is also suggestive that patients entering the PPS state are not homogeneous, with about 30% subject to a better PPS than other patients).

However, the equivalent PPS survival time of individual patients does not mean that there is no difference in overall mean PPS between trial arms. This is because PFS is a compound variable (indicating either death or disease progression can have occurred); differences between trial arms can occur so that different proportions of PFS patients who die prior to confirmation of disease progression may affect the balance between the trial arms in the number of patients entering the post-progression state.

Examination of the NAPOLI-1 trial data show that such a difference is present: [redacted] of progression events in the 5-FU/LV arm are deaths compared with [redacted] in the nal-iri+5-FU/LV arm, indicating that more patients in the latter arm will survive to enter the PPS health state. Applying these proportions to the trial arms separately results in estimates for PPS of 3.604 months for patients treated with 5-FU/LV versus 3.815 months for patients treated with

nal-iri+5-FU/LV, an advantage of 0.210 months in favour of patients treated with nal-iri+5-FU/LV.

This finding suggests that the method used in the company model to estimate survival trends, namely by log-normal parametric models, and then assuming that PPS can be reliably calculated as the simple difference between OS and PFS, is flawed and unreliable in this case.

Overall survival

There are three approaches that may be followed to estimate the mean OS benefit which may be expected from treatment with nal-iri+5-FU/LV compared to 5-FU/LV:

1) Simple K-M calculation of the estimated mean survival in each trial arm without recourse to any modelling or extrapolation. This is potentially unbalanced as the trial data are complete for the nal-iri+5-FU/LV arm but exhibit a single patient still alive and at risk in the 5-FU/LV arm

2) Use K-M OS data directly in both trial arms, but model the likely survival experience of the final patient in the 5-FU/LV arm by extrapolation

3) Apply the method described above of estimating OS by addition of survival in the PFS and PPS states, extrapolating PFS for the single surviving pre-progression patient in the 5-FU/LV arm, and taking account of the differential in death rates included within the recorded progression events.

The differences between the results obtained by these three methods, and the company model serve to illustrate the extent of uncertainty associated with estimating trial-based OS estimates.

Method 1: Simple K-M OS calculation

The K-M estimated means for the recorded OS data from the NAPOLI-1 trial, are 7.178 months for patients treated with 5-FU/LV and 9.391 months for patients treated with nal-iri+5-FU/LV, giving a net OS gain of **+2.212 months** (95% CI 0.173 to 4.251). This may be compared with the base case company model estimated mean gain of 2.503 months.

Method 2: K-M OS data with extrapolation for the final patient in the nal-iri+5-FU/LV arm

The K-M estimated mean for the recorded OS data from the NAPOLI-1 trial for patients treated with nal-iri+5-FU/LV is 9.391 months. Figure 12 shows trial OS data together with the

ERG long-term exponential survival trend applied to the 5-FU/LV arm from 28.4 months. This yields an estimated mean OS for patients treated with 5-FU/LV of 7.584 months and a net mean OS gain of **+1.807 months** attributable to treatment with nal-iri+5-FU/LV. Details of the ERG's exponential extrapolation are outlined in Appendix 11.9.

Method 3: Addition of estimates of PFS and PPS, adjusting for differential death rates, and extrapolating PFS for the final patient in the nal-iri+5-FU-LV arm

This method involves using the K-M estimates of mean PFS for each trial arm (which are each based on complete trial data), to which is added the estimated time in the post-progression state based on the pooled K-M data analysis (Figure 11) adjusted for the proportion of patients experiencing a non-fatal progression event as described above.

For the 5-FU/LV arm, this yields mean estimates for PFS (3.142 months), PPS (3.604 months) and OS (6.746 months). Similarly, in the nal-iri+5-FU/LV arm mean estimates are PFS (5.677 months), PPS (3.815 months) and OS (9.491 months), so that the net mean OS gain is +**2.745 months** attributable to treatment with nal-iri+5-FU/LV.

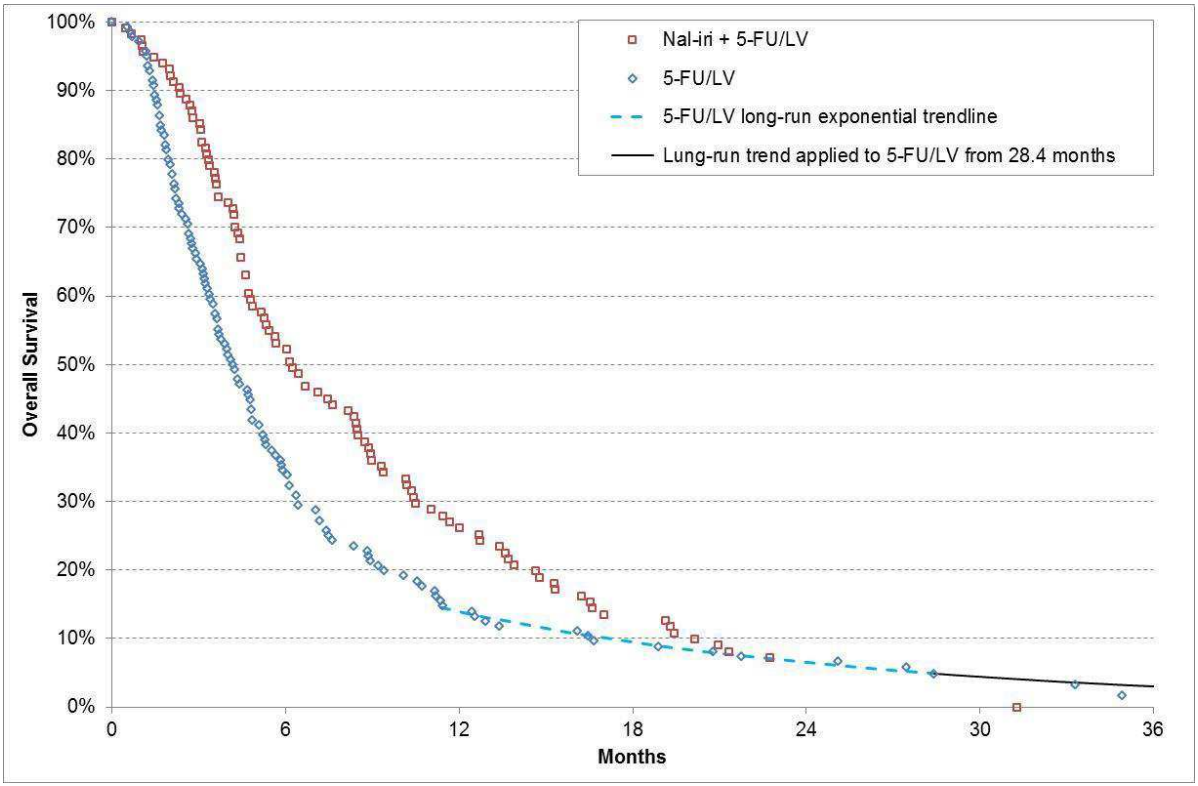

Figure 12 NAPOLI-1 OS K-M data, with ERG long-term extrapolation for patients treated with 5-FU/LV

Summary: The ERG has employed three different methods to estimate the mean survival gain shown in the NAPOLI-1 trial arising from treatment with nal-iri+5-FU/LV rather than 5-

FU/LV. The estimates range from 1.807 months (Method 2) to 2.212 months (Method 1) and 2.745 months (Method 3); these can be compared to the company's log-normal models yielding a mean OS gain of +2.503 months. Though each of the ERG methods has some merit, the ERG prefers Method 2, on the grounds that Method 1 is easily biased by non-equivalent cut-off points for estimating partial 'area under curve' totals, and Method 3, though technically valid, has been found sometimes to be liable to greater sensitivity to parameter uncertainty.

A summary of OS estimates disaggregated by PFS and PPS estimates generated using the company model, and the ERG's preferred approach is presented in Table 53. In all cases, the implementation of the ERG's preferred approach to modelling survival results in less optimistic predictions than those generated using the company's approach. The PPS estimates for both nal-iri+5-FU/LV and 5-FU/LV using ERG assumptions are reduced considerably, and the net mean difference in PPS is more in favour of 5-FU/LV compared to the company model.

However, it must be noted that in both the company model and the ERG's preferred approach the estimates of PPS are anomalous and inconsistent with the finding that each patient entering the post-progression state has an equal prospect of additional survival time prior to death. In addition, the observed difference in the proportion of patients suffering a fatal progression event would be expected to generate a survival gain (not a loss) as a consequence of having previously been treated with nal-iri+5-FU/LV. Nonetheless, it can be concluded that the survival benefit associated with nal-iri+5-FU/LV arises predominantly prior to disease progression, which is consistent with the observation that PPS K-M data indicate that there is no additional benefit following progression.

Table 53 Company and ERG mean survival estimates

Treatment	PFS (months)	PPS (months)[#]	OS (months)
Company approach			
Nal-iri+5-FU/LV	5.472	4.697	10.169
5-FU/LV	2.815	4.851	7.666
Difference	**+2.657**	**-0.154**	**+2.503**
ERG preferred approach			
Nal-iri+5-FU/LV	5.677	3.714[#]	9.391
5-FU/LV	3.142	4.442[#]	7.584
Difference	**+2.535**	**-0.728[#]**	**+1.807**

PFS=progression-free survival; PPS=post-progression survival; OS=overall survival; # for consistency, ERG PPS figures are calculated as the difference between OS and PFS estimates.
Source: Company model and ERG calculations

Time on treatment

The company's approach to modelling the time on treatment trial data systematically under-estimates overall time on treatment for patients in both arms of the NAPOLI-1 trial, especially during the first 15 months from randomisation (Figure 13). Additionally, the fitted models continue to accrue additional treatment time long after the last patient in the trial had ceased treatment (after 29 months for nal-iri+5-FU/LV and 16 months for 5-FU/LV), due to the long tails of the log-normal distribution. Overall, the company models underestimate time on treatment in the 5-FU/LV arm by 15%, and in the nal-iri+5-FU/LV arm by 1.4%.

Since the trial data for this outcome are complete, there can be no justification for extrapolating beyond the trial duration, nor indeed for modelling this variable at all.

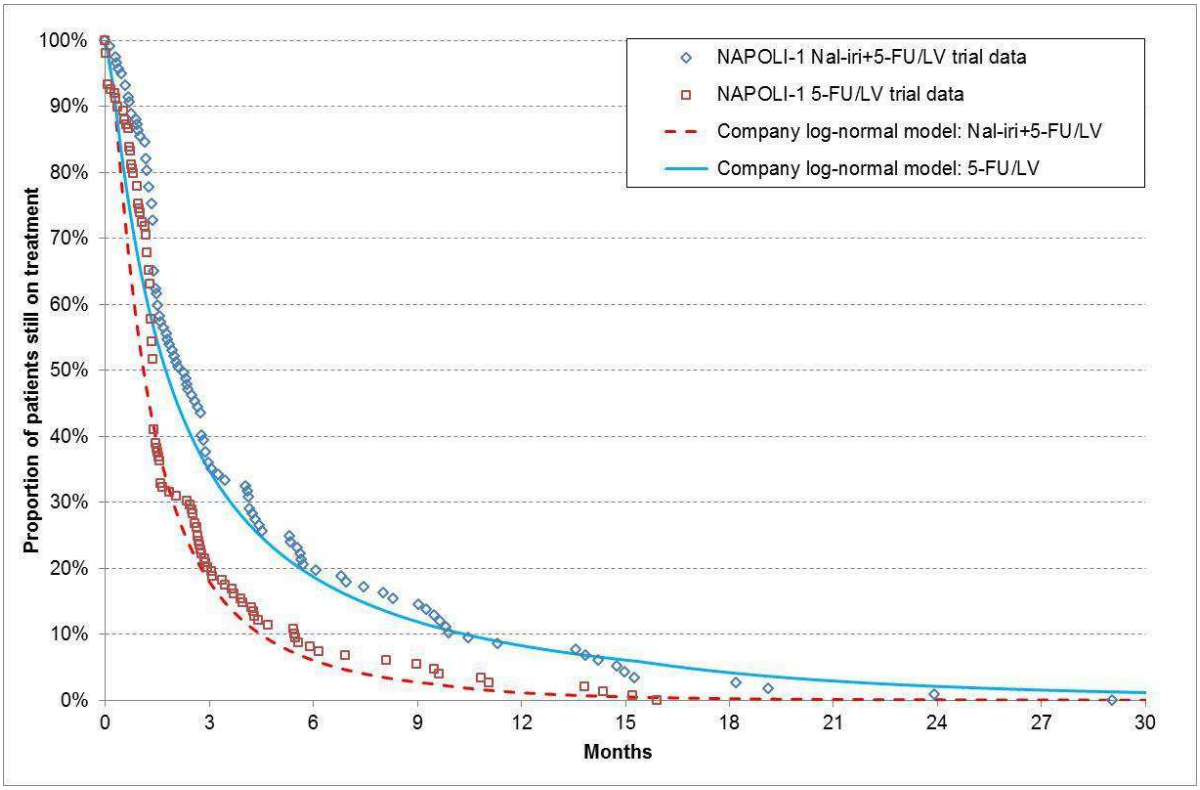

Figure 13 Patients on treatment: company projections and K-M data

For the comparison of treatment with nal-iri+5-FU/LV versus 5-FU/LV, the application of time to treatment data from the NAPOLI-1 trial increases the company's base case ICER per QALY gained by nearly £2,000 per QALY gained (see Table 59).

Time on treatment: oxaliplatin+5-FU/LV

To represent PFS and OS for patients treated with oxaliplatin+5-FU/LV, the company adjusted the parametric curves used to model PFS and OS for patients treated with nal-iri+5-FU/LV, using HRs generated by their ITC. However, to model time on treatment, the company assumed that patients treated with oxaliplatin+5-FU/LV remained on treatment for the same length of time as patients treated with nal-iri+5-FU/LV in the NAPOLI-1 trial (CS page 129). No rationale was provided for this assumption.

Thus, the company model uses the same log-normal curve to model pre-progression treatment for patients treated with nal-iri+5-FU/LV and for patients treated with oxaliplatin+5-FU/LV. This results in the proportion of patients receiving oxalipatin+5-FU/LV, who are in the 'pre-progression on treatment' state at 22 weeks, exceeding the proportion of patients in the PFS state. The company uses a model correction to resolve this issue by over-riding the trial time on treatment data with PFS data when it appears that there are more patients on treatment than remain alive in PFS. **The need for the company to apply an arbitrary model correction highlights that, for the population of patients receiving oxaliplatin+5-FU/LV, either the method used to represent PFS or the method used to represent pre-progression on treatment must be incorrect.** The ERG considers that the company's assumption that the duration of exposure to treatment is the same for patients treated with nal-iri+5-FU/LV as for patients treated with oxaliplatin+5-FU/LV is erroneous. The ERG examined the effect of using the company's pre-progression on treatment curve for patients receiving 5-FU/LV to model the time on treatment for patients receiving oxaliplatin+5-FU/LV to assess the impact of such a change on the ICER estimate.

For the comparison of treatment with nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV, when the time on treatment of oxaliplatin+5-FU/LV is assumed equal to that of 5-FU/LV, this increases the company's base case ICER per QALY gained by £17,692.

5.5.4 Costs of treatments

Dose intensity reductions

In the NAPOLI-1 trial, in cases where treatment resulted in toxicity, some patients missed doses or received reduced doses. In the company model, it is assumed that, as a result of reduced doses or dose omissions, there is a corresponding reduction in drug acquisition costs. Based on data from the NAPOLI-1 trial, the company estimated that, on average, patients prescribed nal-iri+5-FU/LV and 5-FU/LV would receive 85% and 95% respectively of the anticipated licensed dose. The company has assumed that dose reductions for patients receiving oxaliplatin+5-FU/LV are the same as the dose reductions for patients receiving nal-

iri+5-FU/LV (i.e. 85%). In clinical practice, savings from reduced doses of chemotherapy only materialise if each change from the normal dose is known sufficiently in advance to allow the pharmacy department to alter the parenteral formulation. Due to the nature of the administration process, doctors typically see patients on the same day that the parenteral treatment is prepared by the pharmacy department. The ERG considers that although planned treatment alterations can vary between treatment administration sessions, this variation is difficult to anticipate in routine clinical practice, especially in NHS centres treating small numbers of patients. It is important to note that following examination of the CSR and the company's clarification response, the ERG concludes that there are no reductions in LV dosing in any of the NAPOLI-1 trial arms; however, the company's dose intensity reduction in the model is inclusive of LV for all of the treatments.

The ERG considers the case for pro-rata reductions in drug costs to be questionable in an NHS setting and that full costing should be used in the base case analysis to take into account possible wastage. For the comparison of treatment with nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV, use of the full dose increases the company's base case ICER per QALY gained by £10,263 to £95,320 and, for the comparison of nal-iri+5-FU/LV versus 5-FU/LV, the effect is to increase the company's base case ICER per QALY gained by £16,355 to £148,701.

Body surface area and acquisition of generic drugs

In the company model, a mean BSA value of 1.79 per m^2 was taken from the study by Sacco et al[39] for adult cancer patients in the UK. The Sacco study[39] presents data for different tumour types and allows gender differences in BSA to be taken into account. The value selected by the company was undifferentiated by tumour type or site and did not take into account the male: female balance of patients participating in the NAPOLI-1 trial. Using the same publication, the ERG identified specific mean BSA values for patients with upper gastrointestinal cancer[39] (1.898 for males and 1.654 for females) and used these to generate weighted acquisition costs for all drugs dosed by BSA. Use of the more relevant BSA value results in increased drug costs for all patients in the company model.

All drugs used in the company model, except nal-iri, are available as generic formulations and so may be sourced relatively cheaply by the NHS. However, the company model substantially overestimates the acquisition cost of the generic drugs by using prices sourced from the BNF[45] and by failing to take advantage of the economic efficiencies that are achievable by using a mixture of different vial sizes.

The Department of Health's electronic market information tool (eMit) provides details of the average prices paid by NHS hospitals in England for generic drugs.[49] These unit costs are thus more reflective of the actual cost of drugs to the NHS than those given in the BNF.[45]

To calculate average drug acquisition costs, the company has estimated the proportion of patients requiring anything from one to 20 vials of each drug in each treatment combination using a normal distribution. The mean number of vials used in the calculation of the normal distribution was derived from the required dose per m^2, mean BSA and the relevant dose intensity modifier. The company has assumed that only one vial size is available for each generic drug: 500mg for 5-FU, 50mg for oxaliplatin and 50mg for LV. In fact, information provided in the eMit[49] database indicates that there are multiple vial sizes available for each of these generic drugs and, as a general rule (although not in every case), the larger the size of the vial, the lower the cost per mg of the drug. The company has chosen the smallest available vial sizes to calculate the cost of the generic drugs and, therefore, ignores the potential savings that can be gained by combining different vial sizes to achieve the required dose. The acquisition cost of nal-iri is based on 50mg vials in the company model and the ERG has not seen any evidence that this drug will be available in any other size vial.

The ERG has re-calculated the average cost per dose of the intervention and the comparators using prices from the eMit[49] database. To take into account the range of vial sizes available for each of the generic drugs, the ERG first used a normal distribution for BSA to estimate the proportion of patients requiring a given dose. The optimum combination of vial sizes for that dose was then determined according to the price per mg of each available vial size. The ERG's revised average cost per dose is the sum of the cost of each dose (optimised by available vial sizes) weighted by the proportion of patients expected to receive each dose.

The price of drugs, and range of available vial sizes according to information in the eMit[49] database, are shown in Table 54. The results of the ERG's re-calculations of average drug costs are shown in Table 55.

Table 54 Drug costs used in the company model: company model versus ERG

Drug name	Vial size	Company model	ERG
		Cost per mg	
Nal-iri	50mg	[redacted]	-
Oxaliplatin	50mg	£3.140	£0.212
	100mg	-	£0.155
5-FU	500mg	£0.012	£0.002
	1000mg	-	£0.001
	2500mg	-	£0.002
	5000mg	-	£0.001
LV (as calcium folinate)	50mg	£0.375	£0.025
	100mg	-	£0.030
	300mg	-	£0.015

ERG=Evidence Review Group; mg=milligram
Source: Company model, eMit, ERG calculations

Table 55 Weekly average treatment costs per patient used in the model: company versus ERG drug acquisition costs using revised BSA value

Item	Company model			ERG (revised BSA)		
Nal-iri+5-FU/LV	Nal-iri	5-FU	LV	Nal-iri	5-FU	LV
Weekly drug cost	[redacted]	£24.97	£118.80	[redacted]	£2.24	£5.19
Weekly treatment cost	[redacted]			[redacted]		
Oxaliplatin+5-FU/LV	Oxaliplatin	5-FU	LV	Oxaliplatin	5-FU	LV
Weekly drug cost	£238.84	£11.35	£61.74	£13.14	£1.19	£2.72
Weekly treatment cost	£311.93			£17.04		
5-FU/LV	5-FU		LV	5-FU		LV
Weekly drug cost	£31.16		£91.27	£2.94		£4.19
Weekly treatment cost	£122.43			£7.12		

BSA=body surface area; ERG=Evidence Review Group
Source: Company model and ERG calculations

Combining the ERG's preferred BSA values and preferred drug acquisition costs in the company model yields an increase in the ICER of nearly £[redacted] per QALY gained for treatment with nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV, and a decrease of more than £[redacted] per QALY gained for nal-iri+5-FU/LV versus 5-FU/LV (£[redacted] and £[redacted] per QALY gained respectively).

Post-progression treatment costs

On page 127 of the CS, it is stated that the company has assumed that the average weekly cost per patient of post-progression treatment is equivalent to the weekly cost of treatment with nal-iri+5-FU/LV. In the company model, the weekly cost of post-progression treatments is equivalent to the acquisition cost of nal-iri ([redacted]) – a price that does not include the cost of 5-FU/LV. Moreover, the cost used in the company model does not include any administration or monitoring costs.

Clinical advice to the ERG is that, in the NHS following failure of second-line therapy patients are unlikely to receive further chemotherapy. In addition, there is no evidence to suggest that the provision of conventional chemotherapy would have any significant impact on survival. The ERG considers that it is more appropriate to assume that, after progression all patients receive best supportive care (BSC) in the form of palliative therapy.

For the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV, use of palliative care rather than the company's post-progression treatment costs decreases the company's base case ICER per QALY gained by more than £[redacted], and for the comparison of nal-iri+5-FU/LV versus 5-FU/LV the effect is to increase the size of the company's base case ICER per QALY gained by £[redacted]. The decrease in the size of the ICER versus oxaliplatin+5-FU/LV is explained by the greater reduction in total costs in the nal-iri+5-FU/LV arm as a result of a longer time spent in PPS compared to the oxaliplatin+5-FU/LV arm.

Adverse event costs

As part of the clarification process, the ERG requested NAPOLI-1 trial grade 3 or higher treatment related AEs reported by ≥5% of patients. Table 44 of the CS includes details of the costs associated with treating AEs that are used in the company model. The ERG has concerns about the choice of Healthcare Resource Groups (HRG) codes used to cost AEs. The approach taken to determine the cost of treating a patient with grade 3 to 4 diarrhoea was calculated using a weighted average of day case HRG codes, whilst the definition of grade 3 or higher AEs is that they require hospital admission.[50] The ERG considers that the use of the weighted average of costs for all types of admission is more reflective of the costs to the NHS. Using the ERG's revised unit costs per AE (see Table 56), the ICER per QALY gained for treatment with nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV increases by nearly £[redacted], and for treatment with nal-iri+5-FU/LV versus 5-FU/LV the ICER increases by nearly £[redacted] per QALY.

Table 56 Unit cost of AEs: company model and ERG amendments

Adverse Event	Unit cost per AE		HRG code	Admission type	
	Company model	ERG		Company model	ERG
Anaemia	£528.15	£405.47	SA04L, Iron Deficiency Anaemia with CC score 0-1	Non-elective short stay	Weighted over all admissions
Neutropenia	£127.70	£127.70	XD25Z Neutropenia drugs band 1, NHS Trusts High Cost Drugs	n/a	n/a
Abdominal pain	£387.25	£752.10	FZ90A - FZ90B. Weighted average of Abdominal Pain with Interventions and without Interventions	Regular Day or Night Admissions	Weighted over all admissions
Diarrhoea	£319.34	£2,739.90	FZ49D - FZ49H. Weighted average of Nutritional Disorders with and without Interventions	Day case	Weighted over all admissions
Nausea	£319.34	£2,739.90	Assumed same as diarrhoea	Day case	Weighted over all admissions
Vomiting	£319.34	£2,739.90	Assumed same as diarrhoea	Day case	Weighted over all admissions
Fatigue	£44.00	£1,848.00	1 nurse visit per day (£44) for duration of event	1 day	42 days*

AEs=adverse events; ERG=Evidence Review Group; HRG=healthcare resource groups
* Mean duration from company clarification response, Table 22

5.5.5 Health state utility values

The health state utility values used in the company model are based on those presented in a US study by Romanus et al[51] (0.8 for progression-free survival and 0.75 for post-progression survival). Previously, these values have been used in the company model submitted during the appraisal of nab-paclitaxel in combination with gemcitabine for previously untreated metastatic pancreatic cancer (TA360).[13] These values were amended (by the ERG involved in that appraisal) to make them more relevant for use in a UK patient population; the amended values were 0.742 and 0.671 for the progression-free health state and for the progressed health state respectively.[41]

The Romanus study[51] was conducted in first-line patients with advanced pancreatic cancer. Patients in this study[51] had an ECOG PS of 0 to 2 and received gemcitabine plus placebo or gemcitabine plus bevacizumab as a first-line treatment. The ERG considers that utility values derived from a first-line patient population are likely to overstate patient quality of life when applied to a second-line patient population. Furthermore, there is considerable uncertainty regarding the appropriateness of using Romanus[51] based utility values as the values for patients with stable disease were similar to those for the age-matched US general population.

The ERG considers that the pre-progression and post-progression health state utility values of 0.742 and 0.671 used in the company model overestimate patient HRQoL. Moreover, the utility values derived from the Romanus study[51] accounted for treatment related AEs arising

from active chemotherapy. The separate addition, by the company, of disutility values associated with AEs results in double counting of treatment related disutility.

The ERG considers the use of the progressed disease health state utility value used in the ERG TA360 report[41] (0.671) to be a more accurate reflection of the quality of life of patients in the population of interest who are in the progression-free state than the value used by the company (0.742). The ERG considers that a value of 0.6 should be used to represent quality of life for patients in the post-progression health state. This value was presented in a study reporting results from the phase III RAINBOW trial,[52] and was derived from patients with locally advanced or metastatic gastric cancer receiving second-line combination chemotherapy. It is important to note that this value was obtained from patients upon progression/end of treatment and does not take into account further deterioration in health following progression. Patients in the RAINBOW trial[52] had similar demographic characteristics to those in the NAPOLI-1 trial. In that trial,[52] EQ-5D index scores were elicited using the time-trade off (TTO) method and were calculated using UK population-based preference weights from the study by Dolan.[53] The various utility value options are presented in Table 57.

For the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV, the use of the ERG's preferred health state utility values, increases the company's base case ICER per QALY gained by more than £10,000, and for the comparison of nal-iri+5-FU/LV versus 5-FU/LV the effect is to increase the size of the company's base case ICER per QALY gained by nearly £16,000.

Table 57 Utility value options

Source	PFS	PPS
Romanus study[51] - US values	0.80	0.75
ERG report for the appraisal of nab-paclitaxel in combination with gemcitabine for previously untreated metastatic pancreatic cancer (TA360)[41] & company submission	0.742	0.671
ERG's preferred values	0.671	0.60

PFS=progression-free survival; PPS=post-progression survival

5.5.6 Terminal disutility

The company model does not include the effects of terminal disutility on patient quality of life. The ERG has estimated the mean EQ-5D utility during the 4 weeks before death to be 0.146 using results from the study by Van den Hout et al.[54] This study involved collecting utility values from patients receiving palliative care for advanced lung cancer, observing rapid declines in in average EQ-5D utility in the weeks leading up to death. The ERG

recognises that these utility values relate to patients with lung cancer but, to the ERG's knowledge, this is the only study available presenting utility data derived from patients who are only receiving palliative care for advanced cancer.

For the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV, the application of the terminal disutility, increases the company's base case ICER per QALY gained by about £[redacted] and the effect on the comparison of nal-iri+5-FU/LV versus 5-FU/LV decreases the size of the ICER per QALY gained by about £[redacted].

5.5.7 Minor issues of concern

The ERG has identified a further seven areas of concern with regards to the company's cost effectiveness evaluation. The impact of ERG changes to rectify these concerns has not been included in the ERG's cost effectiveness results tables (Section 6, Table 58 and Table 59) as their impact on the size of any of the estimated ICERs per QALY gained is minimal.

5-FU dose in oxaliplatin+5-FU/LV treatment arm

The company assume that the dose of 5-FU in the oxaliplatin+5-FU/LV treatment arm to be 1000mg/m^2 every 2 weeks. This dose for 5-FU was not provided with any justification. According to the company clarification response and clinical advice received by the ERG, in current UK clinical practice, the most common dose of 5-FU in combination with oxaliplatin and LV is 2400mg/m^2 (mFOLFOX6). Implementing the dose change in the company model results in a decrease of £[redacted] to the ICER (£[redacted] per QALY gained) for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV.

Terminal care cost

The submitted company model includes terminal care costs for the final 4 weeks before patient death. The ERG considers these costs to be an underestimate of the true costs incurred during routine clinical practice in the NHS. In the model, it is assumed that 50% of patients receive three home visits by a nurse every week and 50% receive daily care at a hospice/palliative care unit. The company's assumptions do not take into account the additional costs incurred by patients who die in hospital/hospice nor do they include the costs of intensive community palliative nursing, additional drugs and equipment. The ERG has estimated terminal care costs to be £4,103 per patient or £1,026 per week. These costs were derived using mean hospital stay data for malignant gastrointestinal tract disorders[46] and terminal care resource use data from the study by Taylor et al.[55] Costs include in-patient costs for terminal care in hospital, costs for death in hospital and costs for death at home (including GP home visits, community nurse visits, Macmillan nurse visits and additional

drugs and equipment). Implementing this amendment in the company model had no impact on the size of the estimated ICERs per QALY gained as they occur equally to all patients in both treatment arms.

Treatment administration: pharmacist costs

Although a pharmacist cost for each infusion is included in the parameters worksheet in the company model and in the CS (page 125), this cost is not incorporated in the calculation of treatment administration costs. The cost of 15 minutes of pharmacist time required for the preparation of infusion based chemotherapies is in line with the parameters already defined in the company model and those used in the appraisal of nab-paclitaxel in combination with gemcitabine for previously untreated metastatic pancreatic cancer (TA360).[13] Including the cost of pharmacist time results in an increase of £11 per infusion to treatment administration cost.

For the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV, the inclusion of pharmacist costs, increases the company's base case ICER per QALY gained by £[redacted] and the effect on the ICER per QALY gained for the comparison of nal-iri+5-FU/LV versus 5-FU/LV is to increase it by £[redacted].

Treatment administration: infusion disconnection costs

It is stated in the CS (page 124) that, because of the long infusion time required to deliver 5-FU, an additional cost of £97.14[46] has been applied to account for resource use associated with the patient's return to hospital for removal of the cannula and that this cost is independent of infusion time. On clinical advice, the ERG has estimated that approximately 90% of patients would receive a home visit from a community nurse to disconnect this type of infusion pump, and that this visit would take about an hour of nurse time, including travel. This means that only 10% of patients would be likely to attend an outpatient clinic to have their infusion pump removed. Substituting nurse home visits for 90% of patients results in an average total cost of £49.31 per patient for infusion removal.

For the comparisons of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV and versus 5-FU/LV, applying this adjustment in the company model results in reducing the company's base case ICERs per QALY gained by £[redacted] and £[redacted] respectively.

Adverse event disutility

The company has included the effects of selected grade 3+ AEs on HRQoL in their model, namely anaemia, neutropenia, abdominal pain, diarrhoea, nausea, vomiting and fatigue. Disutility values have been obtained from studies by Doyle et al[42] and Nafees et al[44] (both

studies relate to patients with lung cancer) and from Swinburne et al[43] who elicited health state utilities from patients with renal cell carcinoma. The Doyle[42] and Swinburne[43] studies included patients with a mean age that is less than 45 years and did not include patients with metastatic pancreatic cancer. The inclusion of disutility estimates from different patient populations and varying treatment contexts results in an unpredictable bias. The ERG is not able to assess the potential size of this problem due to lack of data.

UGT1A1*28 allele testing

*UGT1A1*28* allele testing is not currently provided as standard care in NHS clinical practice. On clinical advice, it is expected that 5% of patients would receive *UGT1A1*28* allele testing in an NHS setting and such testing is likely to incur additional resource use and training costs; however, the ERG does not consider that these costs would have a substantial impact on the size of the estimated ICERs per QALY gained.

Probabilistic sensitivity analysis

The company's PSA has misrepresented the uncertainty in the submitted model in two ways: by assuming that all parameters are independent of one another and by incorrectly calculating the PSA ICERs per QALY gained.

Parameter values

The company has taken the simplest approach to performing a PSA, which is to assume that all parameters are independent and so vary randomly according to their own distributions without relying on the value of any other parameter. The ERG considers that it is unlikely that all of the parameters are independent, and that it is possible to account for at least some of the parameter dependencies. For instance, the ERG considers it implausible for post-progression utility values to be higher than pre-progression utility values. If pre-progression utility values are already known, then it is also known that post-progression utility values will, at the very least, not be greater than pre-progression values. So, if pre-progression utility values are known, some of the uncertainty in the post-progression utility values can be removed by building this logical relationship into the model. Another way to reduce uncertainty would be to use the Cholesky decomposition, which takes takes into account correlation between the elements in a regression equation used to derive the parameters of a parametric survival curve.

Calculation of ICERs

The company has overestimated the probabilistic ICERs per QALY gained by taking an average of all ICERs produced by the PSA (a 'mean of ICERs') instead of using the mean of incremental costs and mean of incremental QALYs taken over all iterations to derive a single ratio (an 'ICER of means'). Using an ICER of means approach, the company's PSA ICER per QALY gained is reduced from £[redacted] to £[redacted] for the comparison of treatment with nal-iri+5-FU/LV versus 5-FU/LV and from £[redacted] to £[redacted] for the comparison of treatment with nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV. Compared with the mean of ICERs method, the ICER of means method yields probabilistic ICERs per QALY gained for both comparisons that are closer to the company's deterministic ICERs per QALY gained. This indicates that there is less uncertainty in the model (based on the parameters the company has chosen to vary) than is actually suggested by the PSA ICERs reported in the CS.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The ERG identified an error in the value used in the company model to represent baseline utility during the post-progression survival state of the model (0.672 was used instead of 0.671). All of the ICER per QALY gained estimates generated by the ERG have been calculated using the value of the company base case that results following correction of this error.

Table 58 and Table 59 show the effects of the various ERG amendments, both individually and simultaneously, on the size of the company's base case ICERs per QALY gained for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV and nal-iri+5-FU/LV versus 5-FU/LV respectively. The ERG has only implemented changes that have a major impact on the size of the ICERs per QALY gained and has not included changes relating to minor issues (i.e. those described in Section 5.5.8).

The ERG considers that the results (HRs) from the ITC used by the company to facilitate a comparison of the cost effectiveness of treatment with nal-iri+5-FU/LV versus oxaliplatin+5FU/LV are unreliable. The ERG cautions that the ICERs per QALY gained for this comparison are also unreliable and should not be used to inform decision-making. However, to aid decision making, the ERG has generated a range of cost effectiveness results for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV based on assumptions that treatment with oxaliplatin+5-FU/LV results in 10% more, 10% fewer or an equal number of QALYs to treatment with nal-iri+5-FU/LV. These results are presented in Table 60.

Details of the Microsoft Excel revisions made by the ERG to the company model are presented in the Appendices to this ERG report (Section 11.10) and are also included in the ERG amended cost effectiveness model.

Table 58 Cost effectiveness results (nal-iri+5-FU/LV vs oxaliplatin+5-FU/LV): ERG revisions to company base case comparison

Model scenario ERG revision	Nal-iri+5-FU/LV			Oxaliplatin+5-FU/LV			Incremental			ICER	
	Cost	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**£/QALY**	**Change**
****Original CS base case***	[redacted]	***0.564***	***0.847***	***£13,975***	***0.362***	***0.535***	[redacted]	***+0.201***	***+0.312***	[redacted]	--
A. Company base case**	[redacted]	***0.563***	***0.847***	***£13,975***	***0.362***	***0.535***	[redacted]	***+0.201***	***+0.312***	[redacted]	--
R1. 5-FU/LV pre-progression time on treatment curve for oxaliplatin+5-FU/LV	[redacted]	0.563	0.847	£10,416	0.362	0.535	[redacted]	+0.201	+0.312	[redacted]	[redacted]
R2. Full dose intensity	[redacted]	0.563	0.847	£15,082	0.362	0.535	[redacted]	+0.201	+0.312	[redacted]	[redacted]
R3. ERG BSA & drug acquisition costs	[redacted]	0.563	0.847	£9,773	0.362	0.535	[redacted]	+0.201	+0.312	[redacted]	[redacted]
R4. ERG post-progression treatment costs	[redacted]	0.563	0.847	£11,034	0.362	0.535	[redacted]	+0.201	+0.312	[redacted]	[redacted]
R5. ERG AE costs	[redacted]	0.563	0.847	£14,957	0.362	0.535	[redacted]	+0.201	+0.312	[redacted]	[redacted]
R6. ERG health state utilities	[redacted]	0.504	0.847	£13,975	0.324	0.535	[redacted]	+0.180	+0.312	[redacted]	[redacted]
R7. ERG terminal disutility	[redacted]	0.552	0.847	£13,975	0.356	0.535	[redacted]	+0.196	+0.312	[redacted]	[redacted]
R8. ERG OS	[redacted]	0.527	0.782	£13,975	0.362	0.535	[redacted]	+0.165	+0.247	[redacted]	[redacted]
R9. ERG PFS	[redacted]	0.565	0.847	£13,975	0.362	0.535	[redacted]	+0.203	+0.312	[redacted]	[redacted]
R10. ERG Time on treatment	[redacted]	0.563	0.847	£13,975	0.362	0.535	[redacted]	+0.201	+0.312	[redacted]	[redacted]
B. R1:R10	[redacted]	**0.465**	**0.782**	**£5,809**	**0.318**	**0.535**	[redacted]	**+0.147**	**+0.247**	[redacted]	[redacted]
C. R2:R10	[redacted]	**0.465**	**0.782**	**£7,838**	**0.318**	**0.535**	[redacted]	**+0.147**	**+0.247**	[redacted]	[redacted]

Costs and QALYs discounted; life years undiscounted
BSA=body surface area; CS=company submission; ERG=Evidence Review Group; QALYs=quality adjusted life years
*Original base case estimate with error **This is the company base case ICER estimate following correction of an error in post progression utility value in company model

Table 59 Cost effectiveness results (nal-iri+5-FU/LV vs 5-FU/LV): ERG revisions to company base case comparison

Model scenario ERG revision	Nal-iri+5-FU/LV			5-FU/LV			Incremental			ICER	
	Cost	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**£/QALY**	**Change**
****Original CS base case***	[redacted]	***0.564***	***0.847***	***£13,338***	***0.429***	***0.639***	[redacted]	***0.134***	***+0.209***	[redacted]	--
A. Company base case**	[redacted]	***0.563***	***0.847***	***£13,338***	***0.429***	***0.639***	[redacted]	***0.134***	***+0.209***	[redacted]	--
R1. ERG OS, PFS, time on treatment	[redacted]	0.529	0.782	£13,655	0.429	0.637	[redacted]	+0.100	+0.145	[redacted]	[redacted]
R1a. ERG OS	[redacted]	0.527	0.782	£13,261	0.426	0.637	[redacted]	+0.101	+0.145	[redacted]	[redacted]
R1b. ERG PFS	[redacted]	0.565	0.847	£12,891	0.431	0.639	[redacted]	+0.134	+0.209	[redacted]	[redacted]
R1c. ERG time on treatment	[redacted]	0.563	0.847	£14,212	0.429	0.639	[redacted]	+0.134	+0.209	[redacted]	[redacted]
R2. Full dose intensity	[redacted]	0.563	0.847	£14,317	0.429	0.639	[redacted]	+0.134	+0.209	[redacted]	[redacted]
R3. ERG BSA & drug acquisition costs	[redacted]	0.563	0.847	£12,436	0.429	0.639	[redacted]	+0.134	+0.209	[redacted]	[redacted]
R4. ERG post-progression treatment costs	[redacted]	0.563	0.847	£6,643	0.429	0.639	[redacted]	+0.134	+0.209	[redacted]	[redacted]
R5. ERG AE costs	[redacted]	0.563	0.847	£13,597	0.429	0.639	[redacted]	+0.134	+0.209	[redacted]	[redacted]
R6. ERG health state utilities	[redacted]	0.504	0.847	£13,338	0.384	0.639	[redacted]	+0.120	+0.209	[redacted]	[redacted]
R7. ERG terminal disutility	[redacted]	0.552	0.847	£13,338	0.418	0.639	[redacted]	+0.135	+0.209	[redacted]	[redacted]
B. R1:R7	[redacted]	**0.465**	**0.782**	**£6,648**	**0.374**	**0.637**	[redacted]	**+0.091**	**+0.145**	[redacted]	[redacted]

Costs and QALYs discounted; life years undiscounted
BSA=body surface area; ERG=Evidence Review Group; OS=overall survival; PFS=progression-free survival; QALYs=quality adjusted life years; TTF=time to treatment failure
*original base case estimate with error **This is the new company base case ICER estimate due to an error in post progression utility value in company model

Table 60 Alternative ICER estimates for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV

Scenario	ICER per QALY gained
Base case	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% less than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% more than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs equal to nal-iri+5-FU/LV	[redacted]
ERG scenario B	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% less than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% more than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs equal to nal-iri+5-FU/LV	[redacted]
ERG scenario C	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% less than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% more than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs equal to nal-iri+5-FU/LV	[redacted]

ERG=Evidence Review Group; QALY=quality adjusted life year; ICER=incremental cost effectiveness ratio

6.1 Conclusions of the ERGs cost effectiveness review

The company's model was constructed according to conventional practice. However, the ERG has concerns about the validity of a number of the model inputs used by the company. The main areas of concern that affect all cost effectiveness comparisons relate to the replacement of complete trial data with parametric survival curves (an approach that adds uncertainty to projections), errors in the methods used to calculate drug costs and use of inappropriate utility values.

In addition, the ERG considers that the company's base case cost effectiveness results for the comparison of nal-iri+5-FU/LV versus oxaliplatin-5FU/LV should be interpreted with extreme caution. Firstly, the lack of effectiveness evidence led the company to use HR results from an ITC to adjust survival projections for patients treated with nal-iri+5-FU/LV to reflect the experience of patients treated with oxaliplatin+5-FU/LV. These HRs are considered by the company and by the ERG to be unreliable. Secondly, as log-normal curves, which are accelerated failure time models, were used to project survival and pre-progression on treatment for patients treated with nal-iri+5-FU/LV, these distributions are not compatible with the proportional hazards assumption and an alternative TR adjustment should have been considered.

The cost effectiveness results that are generated following the application of the ERG's preferred input values are all considerably higher than the range normally considered acceptable by NICE.

7 END OF LIFE

The company puts forward the case (CS, Section 4.13.2.3) that nal-iri+5-FU/LV should be considered under the NICE End of Life criteria, even though it recognises that the gain in median OS reported in the NAPOLI-1 trial does not exceed 3 months which is normally the minimum amount of survival gain required by NICE.[56] The company's reasoning with ERG comment is summarised in Table 61.

Table 61 End-of-life criteria

Criterion	Company statement in support of criteria	ERG comment
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	A systematic review of real-world, peer reviewed, observational European studies [by Carrato 2015[57]] (n=91) found that the median life expectancy at diagnosis was 4.6 months in patients with pancreatic cancer irrespective of stage of diagnosis, and the median survival for patients with metastatic disease was 2.8 to 5.7 months	The ERG concurs that patients with metastatic pancreatic cancer have a life expectancy of less than 24 months
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Median OS was 6.1 months in the nal-iri+5-FU/LV group compared with 4.2 months in the 5-FU/LV group. While the increased survival of 1.9 months is below the 3 months specified in the end-of-life criteria, it represents a 45% increase that would be of substantial benefit to these patients, given the very short life expectancy at diagnosis	The results from the company's economic model suggest that the mean OS gain associated with treatment with nal-iri+5-FU/LV versus 5-FU/LV is 2.5 months. In the ERG amended model the mean survival gain for nal-iri+5-FU/LV versus 5-FU/LV is 1.67 months. The ERG cautions that the OS gain with nal-iri+5-FU/LV compared with 5-FU/LV represents an increase with a treatment that is not commonly used to treat patients with metastatic pancreatic cancer who have progressed following treatment with gemcitabine; a more appropriate comparison would be with oxaliplatin+5-FU/LV. It has not been possible to produce a reliable estimate of the difference in OS between nal-iri+5-FU/LV and oxaliplatin+5-FU/LV. However, the ERG notes that in three RCTs[36,58,59] of oxaliplatin+5-FU/LV, the median OS in the oxaliplatin+5-FU/LV was approximately 6 months, which is similar to that reported in NAPOLI-1 for nal-iri+5-FU/LV. In another RCT of oxaliplatin+5-FU/LV,[17] median OS was lower (3.4 months). It is unclear why the findings in this trial differ so markedly to those from the other trials but this phenomenon may be related to differences in trial and baseline characteristics. **Overall, the OS outcomes for patients treated with oxaliplatin+5-FU/LV reported in these trials are similar in magnitude to the OS outcomes of patients who were treated with nal-iri+5-FU/LV in the NAPOLI-1 trial**
The treatment is licensed or otherwise indicated for small patient populations	The 10-year prevalence of pancreatic cancer in the UK in 2006 was 4349[60]. In 2012 the 5-year prevalence in the UK[61] was 3522	The ERG considers that the anticipated licenced population will be small

OS=overall survival
Source: CS, adapted from Table 34

8 KEY POINTS FOR DECISION MAKERS

8.1 Background

Pancreatic cancer is a condition associated with a particularly high burden of illness since the vast majority of patients present with advanced disease. The outlook for patients with pancreatic cancer has not improved since the 1970s.[62] The median life expectancy at diagnosis is only 4.6 months.[57] Figures published by Cancer Research UK show that there were 7,887 new cases of pancreatic cancer in England in 2013.[5]

Compared with many other types of cancer, there have been relatively few developments in new treatments for patients with metastatic pancreatic cancer. The fluoropyrimidine chemotherapy treatment, 5-FU, has been the mainstay of treatment since the 1950s. Following the approval of gemcitabine for treating metastatic pancreatic cancer in the 1990s, 5-FU became increasingly used as second-line treatment option. More recently it has been used in combination with irinotecan and oxaliplatin (FOLFIRINOX) in the first-line setting and with oxaliplatin (FOLFOX and OFF regimens) as a second-line treatment option following treatment with gemcitabine. FOLFIRINOX, FOLFOX and OFF are not licensed treatments. FOLFOX regimens (mFOLFOX4 or mFOLFOX6) are the most common regimens used in England (~75%). Another treatment option that has emerged for the treatment of second-line metastatic pancreatic cancer and is used in England is capecitabine (~25%), either as a monotherapy or in combination with oxaliplatin.

This appraisal considers the clinical and cost effectiveness nal-iri for use within its anticipated marketing authorisation (CHMP positive opinion is expected circa 21 July 2016), i.e. nal-iri+5-FU/LV for the treatment of metastatic adenocarcinoma of the pancreas, in adult patients who have progressed following gemcitabine-based therapy. The comparators are oxaliplatin+5-FU/LV (e.g. FOLFOX), fluoropyrimidine monotherapy (e.g. 5-FU) and oxaliplatin+capecitabine.

8.2 Clinical effectiveness evidence

Nal-iri+5-FU/LV versus 5-FU/LV

- Direct evidence is only available for the comparison of the effectiveness of nal-iri+5-FU/LV versus 5-FU/LV from the NAPOLI-1 trial; this shows nal-iri+5-FU to be superior in terms of OS and PFS but with a greater number of AEs, notably myelosuppression and gastrointestinal disorders
- Although patients did receive additional treatment on disease progression which may have confounded OS results, the type of treatment received was similar in each arm and there was no treatment crossover from 5-FU/LV to nal-iri+5-FU/LV
- The ERG considers that:
    - except for the usual caveat that goes with nearly all clinical trials that patients tend to younger and fitter than seen in clinical practice, the patient population recruited to the NAPOLI-1 trial is broadly representative of patients with metastatic pancreatic cancer previously received treatment with gemcitabine in clinical practice in England; however, the proportion of patents who received gemcitabine combination therapy was greater than expected in clinical practice in England
    - the trial was generally well designed and conducted with the main potential source of bias being the open-label design
    - the company's OS and PFS HR results are unreliable due to the fact that the approach taken to calculate these values is only valid if the relevant K-M data are proportional to one another; neither the OS nor the PFS K-M data are proportional
    - 5-FU/LV is rarely given to patients who have previously received treatment with gemcitabine.

Nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV

- There is no evidence to allow a direct comparison of the efficacy of nal-iri+5-FU/LV with oxaliplatin+5-FU/LV (the most commonly used regimen in NHS practice for the population of interest)
- The company considered an ITC to be "unfeasible" due to the violation of the PH assumption and trial heterogeneity (in terms of trial location, patient characteristics, prior treatment with gemcitabine [monotherapy versus combination therapy] and length of trial follow-up)
- However, the company considered that results from an ITC were necessary to allow the cost effectiveness of nal-iri+5-FU/LV to be compared with oxaliplatin+5-FU/LV
- The ERG does not consider the results from the ITC to be reliable and so undertook a crude comparison of efficacy and safety data across key RCTs and concluded that, overall, the PFS and OS outcomes for patients treated with oxaliplatin+5-FU/LV reported in these trials are similar in magnitude to the PFS and OS outcomes of patients who were treated with nal-iri+5-FU/LV in the NAPOLI-1 trial.

Other comparators detailed in the final scope issued by NICE

- The company has not provided any evidence to demonstrate the relative effectiveness (or cost effectiveness) of nal-iri+5-FU/LV with oxaliplatin+capecitabine or capecitabine monotherapy.

8.3 Cost effectiveness evidence

Issues relating to the company model

The ERG considers that the structure of the company model (which is constructed according to conventional modelling practice) is appropriate for use in NHS decision-making. However, the ERG has a number of concerns relating to the parameter values used within the model.

Modelling survival

- The company uses log-normal distributions to reflect patient experience (in terms of OS, PFS and TTF) during and beyond the NAPOLI-1 trial period for patients receiving nal-iri+5-FU/LV and those receiving 5-FU/LV. The ERG considers that:
    - trial data, rather than a parametric distribution, should have been used - the company's fitted curves (which are not supported by any biological rationale) only serve to increase uncertainty and may conceal the underlying disease dynamic
    - there is no need for any projection (except for OS for one patient in the 5-FU/LV arm) since the NAPOLI-1 trial was not an ongoing trial but complete
    - the projections made by the company are overly optimistic.
- The company has assumed that the weekly proportion of patients receiving treatment with oxaliplatin+5-FU/LV is the same as that observed for patients in the nal-iri+5-FU/LV arm of the NAPOLI-1 trial. However, at 22 weeks, the proportion of patients receiving oxalipatin+5-FU/LV exceeds the proportion in the PFS state. The company, therefore, incorporated a correction to ensure that the proportion on treatment and the proportion in the PFS were equal from 22 weeks onwards. The ERG considers that:
    - the necessity of employing an amendment suggests that the modelling approach employed by the company is flawed (either in terms of PFS or time on treatment).

Costs

- The NAPOLI-1 trial protocol required that, in cases where treatment resulted in toxicity, patients received reduced doses. In the company model, it is assumed that, as a result of reduced doses, there is a corresponding reduction in drug acquisition costs. The ERG considers that:
    - the case for pro-rata reductions in drug costs to be questionable in an NHS setting and that full costing should be used in the base case analysis.
- In terms of drug costs, the ERG considers that:
    - the company model substantially overestimates the acquisition cost of the generic drugs (oxaliplatin and 5-FU/LV) by using BNF rather than eMiT prices

and by failing to take advantage of the economic efficiencies that are achievable by using a mixture of different vial sizes

- a BSA specific to patients with gastrointestinal cancer, rather than one relating to a more general population of adult patients with cancer, should have been employed to estimate drug costs
- The use of a post-progression treatment cost of £907.43 per week is an overestimate and that it would be more appropriate to assume that patients simply receive BSC.

- The ERG considers that:
  - the terminal care costs used in the company model underestimate the true costs incurred during routine clinical practice in the NHS
  - the utility values used in the company model are overestimates
  - the decrement in quality of life experienced by patients during the final 4 weeks of their life is not captured in the company model.
- The ERG considers that
  - the costs of treating adverse events in the company model underestimate the true costs incurred during routine clinical practice in the NHS
  - the utility values used in the company model are overestimates
  - the decrement in quality of life experienced by patients during the final 4 weeks of their life is not captured in the company model

Other minor issues

- Other minor issues (which have no substantial impact on cost effectiveness results) relate to terminal care costs, treatment administration (pharmacy costs, infusion pump disconnection costs), costs of treating AEs, disutility associated with AEs, *UGT1A1*28* allele testing and the methods used to undertake PSA.

Cost effectiveness of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV

On clinical advice, the ERG considers oxaliplatin+5-FU/LV to be the main comparator in the cost effectiveness evaluation as this treatment is the current standard of care in the NHS. However, the ERG considers results for this comparison to be erroneous due to the lack of reliable clinical effectiveness data. As well as applying ERG's preferred modelling approaches to the company model, the ERG has also explored relative cost effectiveness by generating cost effectiveness results for this comparison by varying the total QALY estimate for the oxaliplatin+5-FU/LV treatment arm.

Cost effectiveness results

The company has submitted a Patient Access Scheme (PAS) application. This is currently undergoing consideration by the PAS Liaison Unit.

For nal-iri+5-FU/LV versus 5-FU/LV, the company's base case ICER increases to £[redacted] per QALY gained following the implementation of all of the ERG's preferred model revisions.

End of life

The treatment is indicated for patients with a life expectancy of less than 24 months and the anticipated licence is for a small population. However, neither the median estimates of OS from the NAPOLI-1 trial nor the estimates of mean life expectancy generated by the company's model or the ERG amended model suggest that treatment with nal-ir+5-FU/LV will lead to an extension of life of an additional 3 months when compared with 5-FU/LV (a comparator that is rarely used in clinical practice). The weight of evidence from the ERG's admittedly exploratory crude comparisons suggests that OS for patients treated with oxaliplatin+5-FU/LV reported in these trials is very similar in magnitude to OS for patients who were treated with nal-iri+5-FU/LV in the NAPOLI-1 trial.

9 OVERALL CONCLUSIONS

Treatment with nal-iri+5-FU/LV appears to be of greater efficacy than 5-FU/LV for patients with metastatic pancreatic cancer who have progressed on treatment with gemcitabine in the NAPOLI-1 trial. Despite an increase in AEs (mostly myelosuppression and gastrointestinal disorder), there appears to be no appreciable deterioration in HRQoL for patients treated with nal-iri+5-FU compared with 5-FU/LV.

The patient population recruited to the NAPOLI-1 trial is, in many respects, representative of patients who would be treated for metastatic pancreatic cancer who progress on treatment with gemcitabine in routine clinical practice in England. It is however noticeable that a greater proportion of patients had received prior gemcitabine combination therapy and fewer patients had received gemcitabine monotherapy than would be seen NHS clinical practice in England. Furthermore, as is common with all clinical trials, the patient population was on average younger and fitter than would be seen in clinical practice, which may explain why a relatively large proportion of patients were receiving study treatment in the third-line (or later) setting.

However, 5-FU/LV is rarely used to treat patients with metastatic pancreatic cancer who have progressed on treatment with gemcitabine. Overall, the PFS and OS outcomes for patients treated with oxaliplatin+5-FU/LV reported in these trials are similar in magnitude to the PFS and OS outcomes of patients who were treated with nal-iri+5-FU/LV in the NAPOLI-1 trial.

The ERG considers that the company's ICERs per QALY gained for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV and 5-FU/LV are underestimated. The ERG identified a number of common issues affecting both comparisons and these are related to the costing methodologies adopted and the estimation of health state utilities as described in the CS. For the oxaliplatin+5-FU/LV comparison, the ERG considers the main issue of concern to be the company's ITC, thus the (corrected) estimated ICER per QALY gained (£[redacted]) is judged to be unreliable. The ERG urges caution when interpreting the cost effectiveness estimates for the nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV comparison. For this comparison, the ERG's revised model estimated ICERs per QALY gained are £[redacted] and £[redacted] for Scenarios B and C, respectively. The ERG performed additional analyses in order to aid decision making in the absence of a reliable ITC effectiveness results.

With regards to nal-iri+5-FU/LV versus 5-FU/LV, the ERG did not consider the company's approach to modelling survival to be appropriate. The ERG disagrees with the use of log-

normal parametric curves instead of mature RCT data from the NAPOLI-1 trial. The ERG amendments to the nal-iri+5-FU/LV versus 5-FU/LV comparison resulted in an ICER of £ [redacted], an increase of more than £[redacted] from the company base case estimate. The ERG does not regard treatment with 5-FU/LV to be a relevant comparator to current UK clinical practice.

9.1 Implications for research

One major limitation is the lack of head-to-head evidence for treatment with nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV. Results from a trial that compares these two treatments could, therefore, help clinical decision making. A trial that compares evidence of the effectiveness of nal-iri+5-FU/LV with either non-liposomal irinotecan monotherapy or in combination with 5-FU/LV (i.e. FOLFIRI) may also be informative.

The reporting of key trial outcome measures for comparator drugs are generally reported in the form of HRs. The fundamental assumption supporting the mathematics used to generate hazard ratios is that hazards remain proportional over time. Examination of the K-M data from the NAPOLI-1 trial indicates that this assumption does not hold for OS or PFS (except in the later stages) data. This renders the HR figures for these two outcome measures as meaningless. Furthermore, the mathematics used in an ITC to generate measures of relative efficacy relies on hazards for each outcome measure being proportional, both within and between, included trials. Again, within the company's ITC not all of these PH assumptions held. The ERG suggests that further statistical research is required to develop methods that can be used:

- to provide a general measure of comparative efficacy in cases where trial outcome data are not proportional
- in the absence of head-to-head trial data, to generate comparative effectiveness results in situations where the PH assumption does not hold.

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11 APPENDICES

11.1 Additional secondary analyses in the NAPOLI-1 trial

Additional analyses were conducted and reported by the company in the CS, as summarised in Table 62. These were secondary outcomes not specified in the NICE scope.

Table 62 Analysis strategy for additional efficacy endpoints in the NAPOLI-1 trial

Endpoint	Definition	Statistical method	Population used for analysis
Tumour marker response	Evaluated by the change in CA19-9 serum levels, which was assessed at treatment start, every 6 weeks thereafter, and at 30 days post follow-up. Response was defined as a decrease of ≥50% of CA19-9 in relation to the baseline level at least once during the treatment period	Tumour marker response rates were pairwise compared using Fisher's exact tests. Time to first tumour marker response was summarised using KM methods	TMRE
CBR rate	CBR is a composite parameter based on four characteristic features of pancreatic cancer: Primary measures of clinical benefit: • Change in pain intensity • Change in analgesic consumption • Change in performance status Secondary measure of clinical benefit: • Change in weight	Objective CBR rates were compared using Fisher's exact tests. Contingency tables for pain classification (analgesic consumption by pain intensity), primary measures of classification (KPS), and overall CBR (primary measures by weight) were presented for each treatment group. Median time to CBR and median duration of CBR were computed using data from patients with CBR	CBRE

CA19-9=Cancer antigen 19-9; CBR=clinical benefit response; CBRE=clinical benefit response evaluable; KM=Kaplan-Meier; TMRE=tumour marker response evaluable
Source: CS Sections 4.3.4, 4.4.3 and 4.4.4

Tumour marker response

The results for tumour marker response for the tumour marker response evaluable (TMRE) population are provided in Table 63. Patients in the nal-iri+5-FU/LV arm were statistically significantly more likely to have reductions of ≥50% from baseline in CA19-9 levels than patients treated with 5-FU/LV alone.

Table 63 Tumour marker (CA19-9) response in the NAPOLI-1 trial – TMRE population

	Nal-iri+5-FU/LV (n=97)	5-FU/LV (n=81)
Tumour marker response, n (%)	28 (28.9)	7 (8.6)
p-value†	p=0.0006	
Median time to first tumour marker response¶, months (95% CI)	4.3 (2.92 to NR)	NR (3.91 to NR)
Log-rank p-value§	p=0.0392	
Wilcoxon p-value§	p=0.0180	

CA19-9=Cancer antigen 19-9; CI=confidence interval; NR=not reached; TMRE=tumour marker response evaluable
†Two-sided p-values from pairwise comparisons of tumour marker response rates using Fisher's exact test.
¶Median time to first tumour response is Kaplan-Meier estimate of the median time to first tumour marker response, in months.
§Two-sided p-values from pairwise comparisons of time to first tumour marker response
Source: CS, Table 23, and company response to ERG clarification letter, question A15

Effect of baseline CA19-9 level on overall survival

An additional analysis was performed to investigate the effect of baseline CA19-9 level on OS. Patients who received study medication and had a recorded baseline CA19-9 measurement were categorised according to baseline CA19-9 measurement, and HRs and corresponding 95% CI were calculated for each quartile. The results, presented in Figure 14, suggest that, compared with 5-FU/LV, nal-iri+5-FU/LV has a greater treatment effect on OS amongst patients with higher CA19-9 levels.

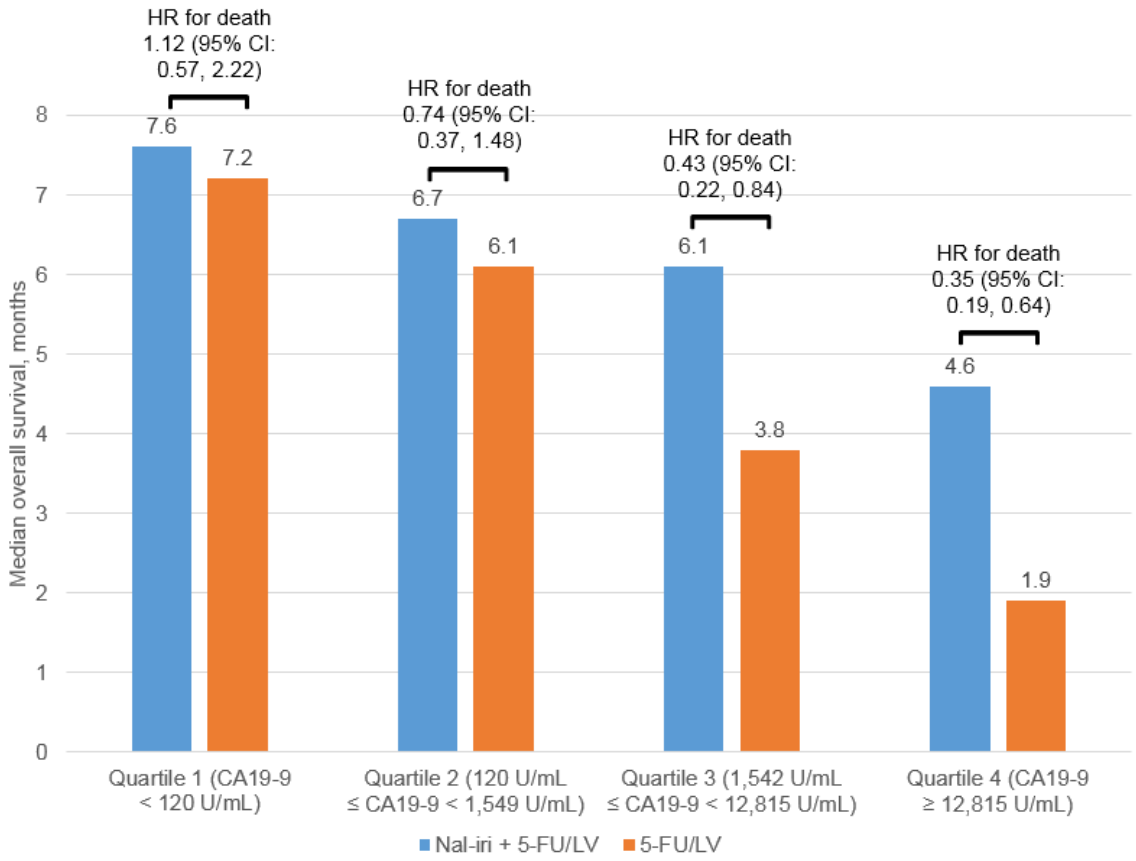


Figure 14 Effect of baseline CA19-9 level on overall survival in the NAPOLI-1 trial – TMRE population

CA19-9=carbohydrate antigen 19-9; HR=hazard ratio

Source: CS, Figure 5

Clinical benefit response

The results of the assessment of Clinical benefit response (CBR) rate are shown in Table 64. The nal-iri+5-FU/LV arm showed a CBR rate of 14.1% compared with 11.7% in the 5-FU/LV arm.

Table 64 Clinical benefit response in the NAPOLI-1 trial – CBRE population

	Nal-iri+5-FU/LV (n=78)			5-FU/LV (n=60)		
Analgesic consumption						
Pain intensity, n (%)	Positive	Stable	Negative	Positive	Stable	Negative
Positive	6 (7.69)	3 (3.85)	3 (3.85)	0	3 (5.00)	2 (3.33)
Stable	2 (2.56)	31 (39.74)	10 (12.82)	2 (3.33)	21 (35.00)	8 (13.33)
Negative	0	5 (6.41)	18 (23.08)	0	7 (11.67)	17 (28.33)
Performance status						
Pain classification, n (%)	Positive	Stable	Negative	Positive	Stable	Negative
Positive	1 (1.28)	9 (11.54)	1 (1.28)	0	4 (6.67)	1 (1.67)
Stable	0	27 (34.62)	4 (5.13)	0	16 (26.67)	5 (8.33)
Negative	0	24 (30.77)	12 (15.38)	0	15 (25.00)	19 (31.67)
Primary measure						
Weight, n (%)	Response	Stable	Non-response	Response	Stable	Non-response
Positive	1 (1.28)	1 (1.28)	0	0	3 (5.00)	0
Non-positive	9 (11.54)	26 (33.33)	41 (52.56)	4 (6.67)	13 (21.67)	40 (66.67)
CBR, n (%)			11 (14.10)			7 (11.67)
p-value						p=0.8007

CBR=clinical benefit response; CBRE=clinical benefit response evaluable
Source: CS, Table 24

The company notes some limitations of the evaluation of CBR, namely that:

- the pain component of the CBR assessment was based on patient-reported daily diary data and diary compliance was low (60% of ITT patients were in the CBRE population); this resulted in a dataset that was highly variable in quality
- the CBR classification rules (CS, Section 4.3.4.2) required observed maintenance of 4 consecutive weeks with robust criteria in each category for classification of improvement, while classification of negative CBR was less robust due to the categorisation of 'any worsening' as negative for pain.

Therefore, the company states that the CBR assessment may detect gross improvements in CBR, but conclusions regarding negative classification should be interpreted with caution.

11.2 Results of company tests for proportional hazards for overall survival in the NAPOLI-1 trial

The results of the tests for PH for the OS endpoint using various analysis populations are provided in Table 65.The results of the performed tests indicated a violation of the PH assumption for all cases, with the exception of the tests using the stratified, ITT population (p=0.1712), and using the ITT population with censoring at change in therapy (p=0.0951).

Table 65 Overall survival: assessments of proportional hazard assumptions in the NAPOLI-1

	Comparison of nal-iri+5-FU/LV versus 5-FU/LV
Unstratified, ITT population	p=0.0169
Unstratified, safety population	p=0.0111
Unstratified, PP population	p=0.0034
Stratified, ITT population	p=0.1712
Censoring at change in therapy, ITT population	p=0.0951
Post-baseline therapy as time-dependent covariate, ITT population	p=0.0162

ITT=intent-to-treat; PP=per protocol
Source: Company response to the ERG clarification letter

11.3 ERG testing of proportional hazards

11.3.1 Proportional hazards testing for NAPOLI-1 trial data

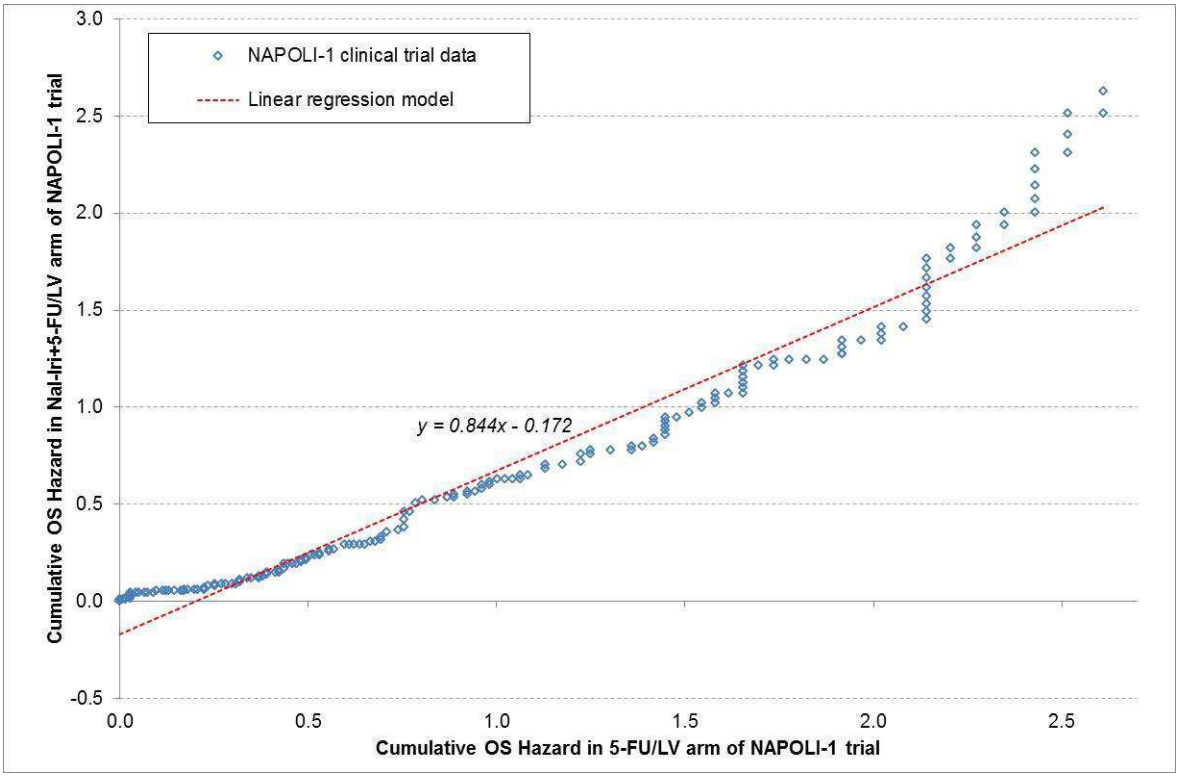
The validity of the PH assumption within the trial is best assessed by considering the H-H plot which shows the relationship between the cumulative hazard for each trial event at common time points in the two trial arms (OS, Figure 15; PFS; Figure 16; TTF, Figure 17). For the PH assumption to be valid, two criteria must be met:

- the data should follow a straight line trend, with individual data points randomly distributed close to and on either side of the trend line
- the linear trend line should pass through the graph origin (zero value on both axes).

Overall survival

Visual inspection of Figure 15 indicates that the NAPOLI-1 results do not support a simple interpretation of the relationship between mortality patterns in the two trial arms. Fitting a simple linear regression model does not generate a reliable representation of the trial data; the model under-estimates mortality hazard in the intervention arm in the early and late phases of the trial, and systematically over-estimates mortality hazard in the intervention arm in the main period of the trial (2.6 – 14 months). It is also noticeable that the linear model estimates a statistically significant deviation from the origin of -0.172 (95% CI: -0.209 to -0.130, $p<0.0001$).

Thus the NAPOLI-1 OS results violate the PH assumption on two grounds: the data show that the HR changes in a non-linear fashion over time, and attempting to estimate a single constant HR results in a relationship which does not conform to the requirement for the trend line to pass through the origin.

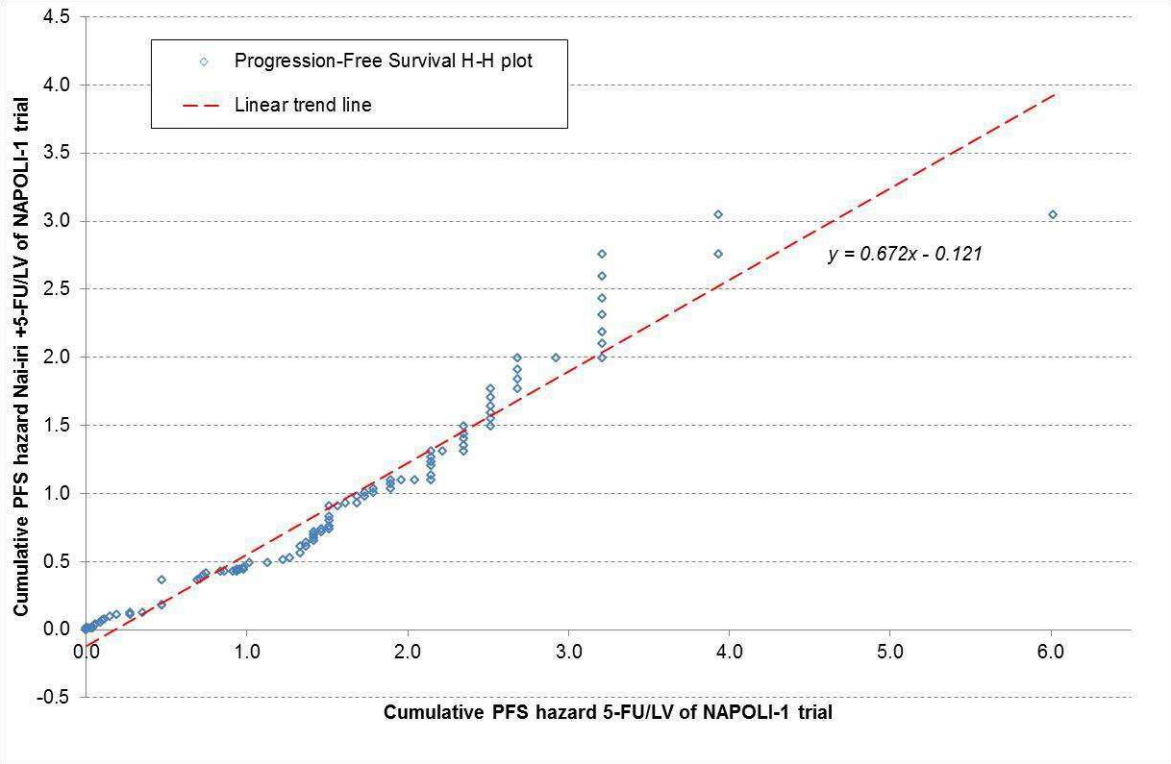


HR=hazard ratio; OS=overall survival

Figure 15 Comparison of alternate trend models for overall survival hazard ratio in the NAPOLI-1 trial

Progression-free survival

Similarly, visual inspection of Figure 16 indicates that the PH assumption is also violated for the PFS data for NAPOLI-1. The linear model under-estimates disease progression hazard in the intervention arm in the early and late phases of the trial, and systematically over-estimates disease progression hazard in the intervention arm in the main period of the trial (1.5 – 8 months). It is also noticeable that the linear model estimates a statistically significant deviation from the origin of -0.121 (95% CI: -0.189 to -0.052, p<0.001).

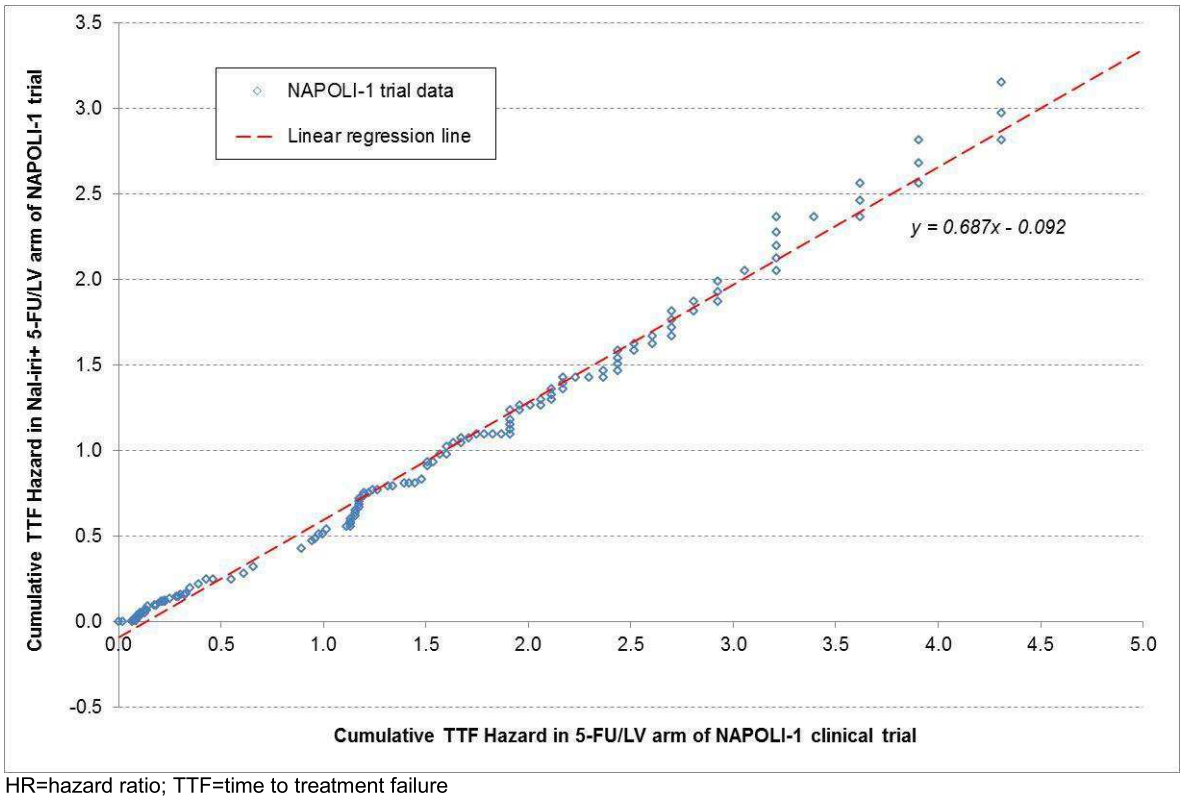


HR=hazard ratio; PFS=progression-free survival

Figure 16 Comparison of alternate trend models for progression-free survival hazard ratio in the NAPOLI-1 trial

Time to treatment failure

Visual inspection of Figure 17 suggests that the PH assumption may be valid for TTF data. However, closer inspection indicates a shallower trend during the first 1.5 months in the intervention arm of the NAPOLI-1 trial, before the long-term linear relationship becomes established. This is confirmed by the small but statistically significant deviation from the origin of -0.092 (95% CI: -0.114 to -0.070, p<0.0001). Thus a simple single HR will tend to progressively understate estimated cumulative treatment failure hazard in the long-term and the PH assumption does not hold.



HR=hazard ratio; TTF=time to treatment failure

Figure 17 Comparison of alternate trend models for time to treatment failure hazard ratio in the NAPOLI-1 trial

11.3.2 Proportional hazards testing for the indirect treatment comparison of nal-iri+5-FU/LV (NAPOLI-1) versus OFF (CONKO-003) and mFOLFOX6 (PANCREOX)

To conduct its cost effectiveness analysis, the company carried out an ITC to compare the effectiveness of treatment with nal-iri+5-FU/LV and treatment with oxaliplatin+5-FU/LV.

The NAPOLI-1 trial: nal-iri+5-FU/LV versus 5-FU/LV

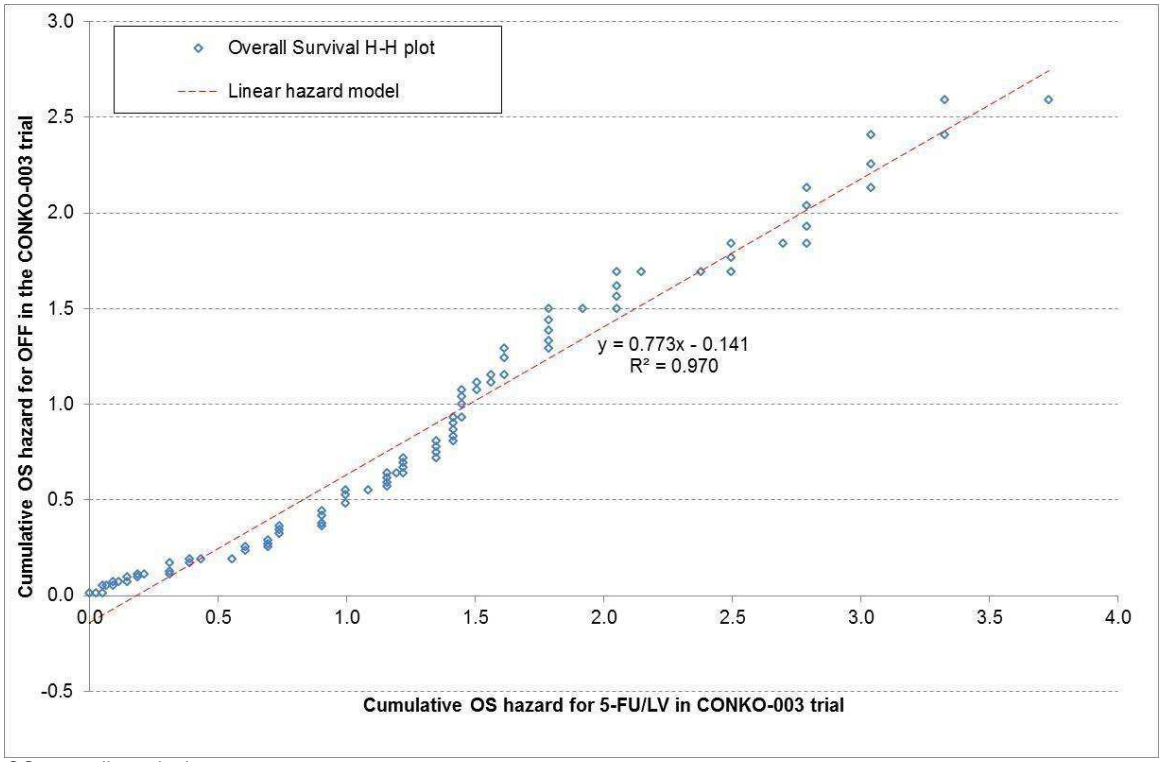
An ITC comparing the effectiveness of nal-iri+5-FU/LV with oxaliplatin+5-FU/LV depends critically on the validity of the PH assumption of treatment nal-iri+5-FU/LV versus 5-FU/LV within the NAPOLI-1 trial. As described in Section 11.3.1, the NAPOLI-1 trial OS and PFS data violate the PH assumption.

The CONKO-003 trial: oxaliplatin+5-FU/LV (OFF) versus 5-FU/LV

In addition, an ITC comparing the effectiveness of treatment with nal-iri+5-FU/LV with oxaliplatin+5-FU/LV depends on the validity of the PH assumption of OFF versus 5-FU/LV within the CONKO-003 trial. Figure 18 indicates that for OS, overall, the linearity assumption is only supportable after about 7.5 months. Prior to this there is a sustained deviation from proportionality. The requirement for the trend line to pass through the origin is not supported by the trial data which indicate a statistically significant negative estimated regression constant of -0.141 (95% CI: -0.187 to -0.096, $p<0.0001$).

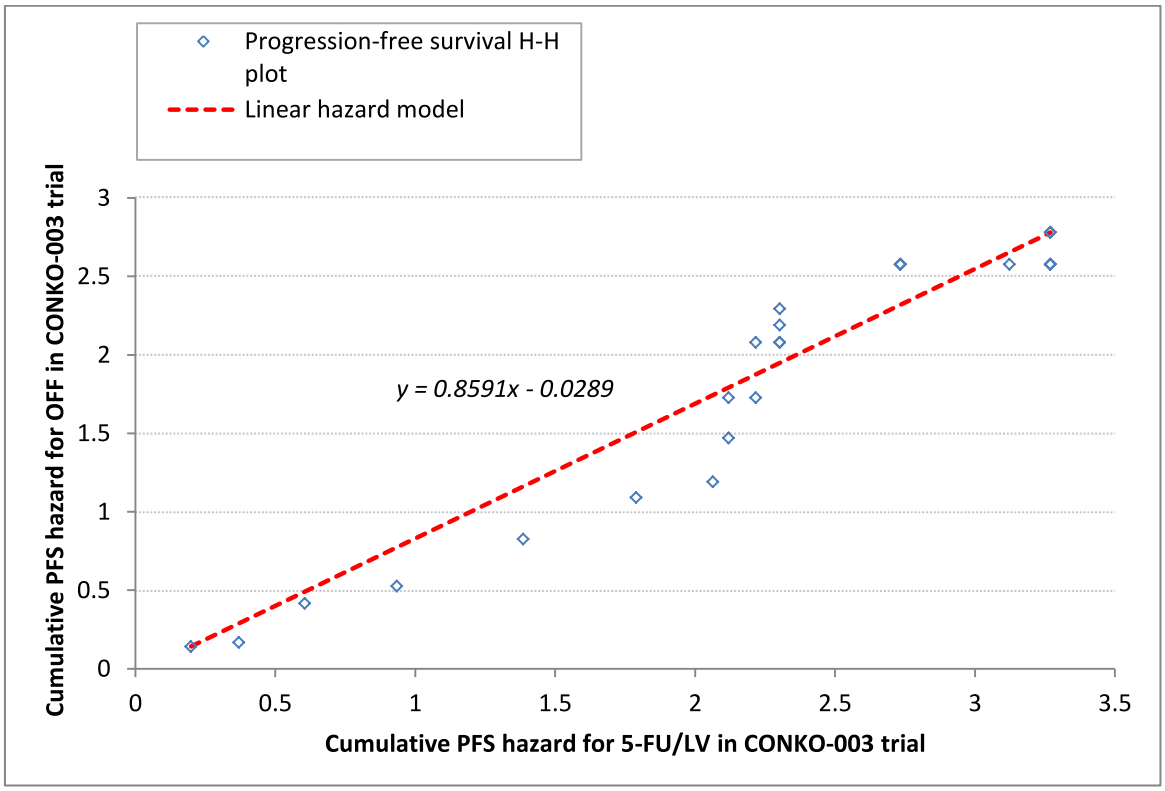
Thus the CONKO-003 trial OS results violate the PH assumption on two grounds: the data show that the HR changes in a non-linear fashion over time, and attempting to estimate a single constant HR results in a relationship which does not conform to the requirement that the trend line should pass through the origin.

Similarly, Figure 19 shows that for PFS, PH is violated as there is sustained deviation from proportionality, indicating that the HR changes in a non-linear fashion over time.



OS=overall survival

Figure 18 Comparison of trial data and a linear trend model for overall survival hazards in the CONKO-003 trial



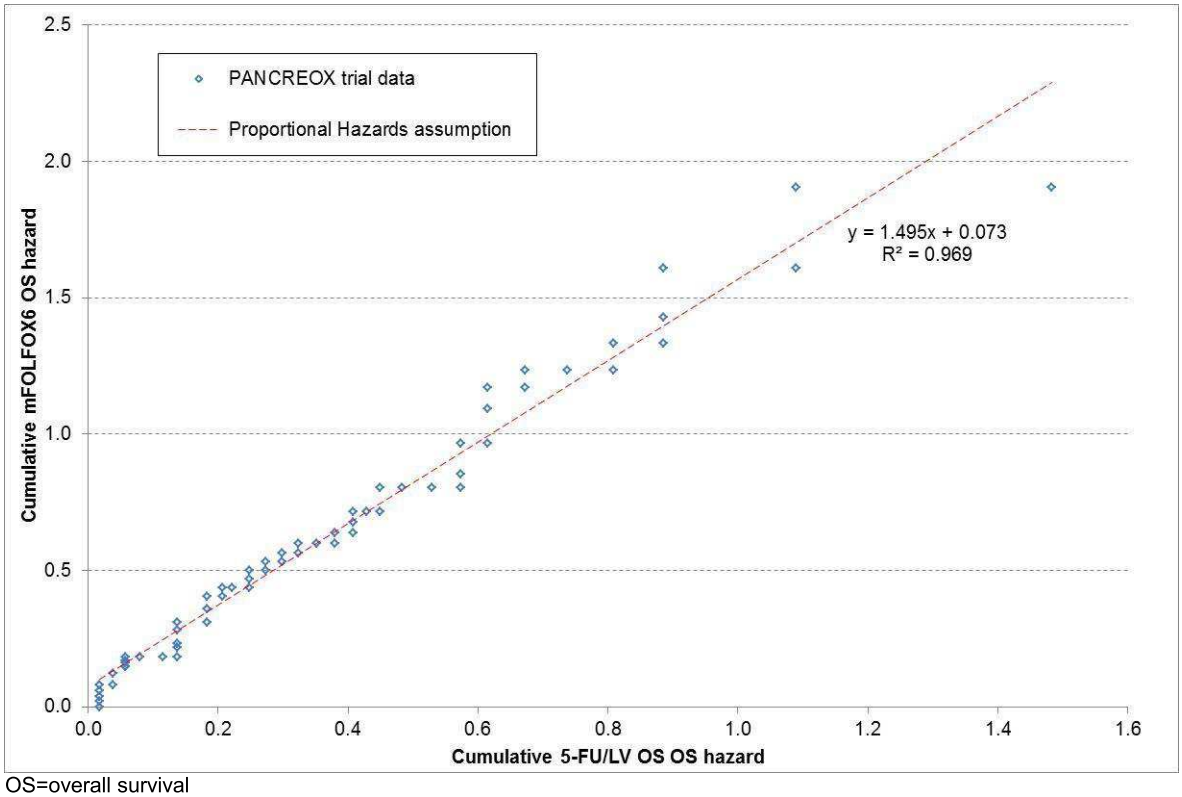
PFS=progression-free survival

Figure 19 Comparison of trial data and a linear trend model for progression-free survival hazards in the CONKO-003 trial

The PANCREOX trial: oxaliplatin+5-FU/LV (mFOLFOX6) versus 5-FU/LV

Figure 20 indicates that overall the linearity assumption may be reasonable in the PANCREOX trial. However, the requirement for the trend line to pass through the origin is not supported by the trial data which indicate a statistically significant positive estimated regression constant of +0.073 (95 %CI: 0.039 to 0.106, p<0.0001). Though this may appear to represent only a minor violation of the PH assumption, it has the potential to propagate a substantial long-term discrepancy when used to generate extrapolated OS estimates in the decision model.

Figure 21 shows that for PFS, the PH assumption is likely to be violated. PFS data deviate substantially from proportionality, indicating that the HR changes in a non-linear fashion over time.



OS=overall survival

Figure 20 Comparison of trial data and a linear trend model for overall survival hazards in the PANCREOX trial

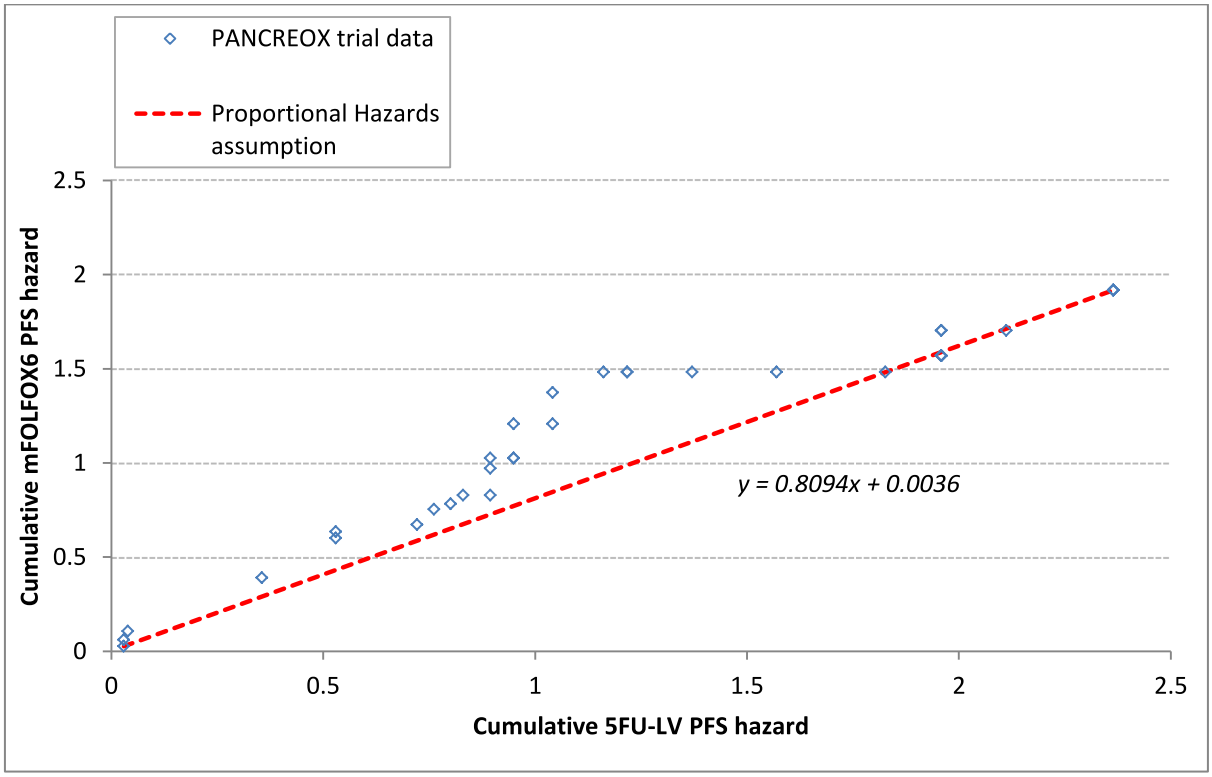


Figure 21 Comparison of trial data and a linear trend model for progression-free survival hazards in the PANCREOX trial

Conclusion

Within each of the three networked trials (NAPOLI-1, CONKO-003 and PANCREOX) the PH assumption is violated for mortality hazards comparing 5-FU/LV with each of the 'active' treatments for both OS and PFS.

In addition, the ITC proposed by the company involve the further assumption that the trial OS data for the common comparator (5-FU/LV) in the three clinical trials are equivalent (i.e. can be assumed to exhibit a HR of 1.0). An examination of the trial data from these three trials indicates that the PH assumption is not valid for these inter-trial comparisons.

The ERG has concluded that the available OS and PFS trial data do not support the use of the PH assumption in estimating HRs. Such HRs cannot be considered reliable and should not be used in populating a decision model comparing nal-iri+5-FU/LV with any of the other treatments in the proposed evidence network.

11.4 Quality assessment of randomised controlled trials included in the company submission

The company's assessment of study quality, i.e. an assessment of risk of bias, is reproduced in Table 66 with ERG comment.

Table 66 Company's quality assessment of the CONKO-003, PANCREOX and NAPOLI-1 trials with ERG comment

Study question	NAPOLI-1	CONKO-003	PANCREOX
Was randomisation carried out appropriately?	Yes. Patients were randomised 1:1 in the nal-iri+5-FU/LV and 5-FU/LV arms by IWRS after all screening assessments were completed and *UGT1A1*28* results were available.	Yes – Patients were randomly assigned to treatment groups using computer-generated random numbers at the study coordination centre.	Unclear – patients were randomised with stratification factors: Age (<70; ≥70 years); Sex ECOG performance score (0; 1; 2); Liver metastases However, the method of randomisation was not described.
ERG comment	Agree	Agree	Agree
Was the concealment of treatment allocation adequate?	Open-label study. Blinding of study treatment was not feasible due to different dosing schedules in the different arms. Using a double-dummy design would result in an unacceptable number of infusions lasting up to 46 hours.	N/A – Open-label trial.	N/A – open-label trial.
ERG comment	Agree	Agree	Agree

Study question	NAPOLI-1	CONKO-003	PANCREOX
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Yes. Patient demographics in both groups were well balanced in terms of sex, race, age and BMI. The nal-iri+ 5-FU/LV and 5-FU/LV groups were also comparable for all baseline disease characteristics, including KPS, albumin level, number and anatomical location of metastatic lesions, measurable metastatic lesions, previous anti-cancer treatment, best response to prior therapy, prior radiotherapy, prior surgery, prior Whipple procedure, has biliary stent, and number and type of concomitant medical conditions (including anaemia, gastrointestinal disorders, fatigue, type 2 diabetes, hypertension, and psychiatric disorders).	The OFF treatment arm had a slightly higher percentage of patients with a better KPS than the FF arm (53.9% with a KPS of 90–100 in the OFF arm versus 47.6% in the FF arm), despite KPS being a stratification criteria prior to randomisation. Median duration of first-line treatment with gemcitabine monotherapy was 4.6 months (95% CI: 3.8 to 6.0) with OFF and 5.3 months (95% CI: 4.4 to 6.0) with FF; hazard ratio 1.03 (95% CI: 0.75 to 1.41). Mean times to start of treatment after random assignment were not significantly different between treatment arms (5.5 days with OFF versus 4.1 days with FF; p=0.10).	Patients in the mFOLFOX6 arm had a longer duration of advanced disease (7.9 months) than patients in the 5-FU/LV arm (5.7 months). In addition, a higher percentage of patients had an ECOG performance score of 2 in the mFOLFOX6 arm (11.1% versus 5.7%), and a lower percentage had ECOG performance score of 0 (13.0% versus 18.9%). A similar proportion of patients had ECOG performance score of 1 in each treatment arm (75.9% in the mFOLFOX6 arm) and 75.5% in the 5-FU/LV arm).
ERG comment	The ERG notes slight imbalances in KPS score and proportion of patients with “other” metastatic lesions between arms. Taken together, the greater proportion of patients with “other” metastatic lesions and patients with KPS 90 in the 5-FU/LV arm could suggest patients were less fit than those in the nal-iri+5-FU/LV arm although the ERG recognises there is a large degree of subjectivity in determining PS. Furthermore, it is noted that the proportion of patients with KPS ≤70 (i.e. the least fit) were similar between arms (8.6% versus 8.4%)	Agree	Agree

Study question	NAPOLI-1	CONKO-003	PANCREOX
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Open-label trial. However, sponsor personnel did not have access to the randomisation code for treatment assignment. In the course of data cleaning and statistical programming development, limited sponsor clinical and biometrics personnel had access to data for individual patients that could be unblinded due to the uniqueness of the visit schedules for each arm. Access to the data in the electronic data capture system was controlled and limited only to authorised personnel for specified data review.	The trial was open-label, but it was not clear whether the outcome assessors were blind to treatment allocation.	The trial was open-label, but it was not clear whether the outcome assessors were blind to treatment allocation.
ERG comment	Agree. The ERG notes that following a protocol amendment, as a result of the new RECIST 1.1 guidelines, [33] central independent confirmation of objective tumour response was no longer required in the trial	Study end points and serious adverse events were centrally evaluated	Agree

Study question	NAPOLI-1	CONKO-003	PANCREOX
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	There was a lower rate of discontinuation with nal-iri+5-FU/LV (88.0%) than with 5-FU/LV (95.0%). This is mainly due to a lower percentage of patients discontinuing due to progressive disease (48.7% versus 53.8%). Other differences were higher discontinuation due to an adverse event (9.4% versus 5.9%), lower discontinuation due to death (1.7% versus 4.2%), and lower discontinuation due to subject decision (12.0% versus 16.0%).	Drop-outs after first treatment administration were not reported.	The withdrawal rate due to an adverse event was 16.3% in the mFOLFOX6 arm and 1.9% in the 5-FU/LV arm. Other drop-outs and adjustments were not reported.
ERG comment	The ERG notes that a greater proportion of patients enrolled in the 5-FU/LV arm (10.9%) never received the treatment they were allocated compared with the nal-iri+5-FU/LV arm (1.7%)	Information on lost to follow-up is reported in Fig 1. There are no unexpected imbalances or drop-outs. The ERG concurs that information on drop-outs after first treatment administration are not reported	The abstract for this paper states that more patients withdrew due to adverse events in the mFOLFOX6 arm (20.4%) than the 5-FU/LV arm (1.9%) and more patients withdrew due to progression in the 5-FU/LV arm (74.1%) than the mFOLFOX6 arm (50.0%). The ERG concurs that other drop-outs and adjustments were not reported. The ERG also notes that a greater proportion of patients received subsequent chemotherapy on disease progression in the 5-FU/LV arm (23.1% than the mFOLFOX6 arm (6.8%)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No.	No.
ERG comment	Agree. However the company explain that not all exploratory analyses are reported in its submission (i.e. biomarker analyses)	Agree.	Agree

Study question	NAPOLI-1	CONKO-003	PANCREOX
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The ITT population was used for the analyses for the primary endpoint (overall survival) and secondary endpoints including progression-free survival. The ITT population was the most appropriate population for these endpoints as it included all randomised patients. The evaluation of tumour marker response used the tumour marker response evaluable population, which only included patients who had elevated CA19-9 level (>30 U/mL) at baseline. The evaluation of clinical benefit response used the clinical benefit response evaluable population, which only included patients who had at least one of: baseline pain intensity ≥20 (out of 100); baseline morphine consumption ≥10 mg/day oral morphine equivalents; baseline KPS of 70–90 points. The evaluation of quality of life used the patient-reported outcome population, which only included ITT patients that provided baseline and at least one subsequent assessment on the EORTC-QLQ-C30 instrument.	The analysis was only performed on the patients that received treatment – 8 patients underwent random assignment but were excluded from analysis before first treatment administration by the steering committee because of withdrawal of informed consent (n=2), lack of progressive disease at baseline (n=1), major GI bleeding that resulted in contraindication of further chemotherapy (n=1), and death before the study started (n=4).	Unclear – it is not reported which population the analyses were performed on.
ERG comment	Agree	Agree but the ERG notes that once a patient had received their first treatment administration, patients who were subsequently lost to follow-up (intervention, n=4, control, n=1) or had a complete response (n=1 in both arms) were included in the analysis	Agree. The ERG however notes that for baseline characteristics, n=54 for both arms and for the analysis of OS, n=54 for both arms

CA19-9=Cancer antigen 19-9; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30= European Organisation for Research and Treatment of Cancer; GI=gastrointestinal; ITT=intention-to-treat; KPS=Karnofsky Performance Status; N/A=not applicable; PS=performance status

11.5 Additional sensitivity analyses of overall survival in the NAPOLI-1 trial

As part of the clarification letter to the company, the ERG requested the results of several sensitivity analyses of OS which were pre-specified in the TSAP. The result of the Wilcoxon test for OS is provided in Table 67.

Table 67 Wilcoxon test result for overall survival in the NAPOLI-1 trial – ITT population

Wilcoxon pairwise comparison of treatments	Two-sided p-value from Wilcoxon test: nal-iri+5-FU/LV versus 5-FU/LV
OS	0.0009

OS=overall survival
Source: Company response to the ERG clarification letter, Table 11

The results for the OS Cox regression model with a time-dependent covariate to account for post-baseline therapy for nal-iri+5-FU/LV versus 5-FU/LV are provided in Table 68.

Table 68 Overall survival Cox regression model with a time-dependent covariate to account for post-baseline therapy in the NAPOLI-1 trial – ITT population

	Nal-iri+5-FU/LV (n=117)	5-FU/LV (n=119)
Patients with change in therapy, n (%)	36 (30.77)	45 (37.82)
Died	22 (18.80)	27 (22.69)
Censored	14 (11.97)	18 (15.13)
Alive	14 (11.97)	17 (14.29)
Lost to follow-up	0	1 (0.84)
Subject withdrew consent from follow-up	0	0
Patients with no change in therapy, n (%)	81 (69.23)	74 (62.18)
Died	53 (45.30)	53 (44.54)
Censored	28 (23.93)	21 (17.65)
Alive	23 (19.66)	10 (8.40)
Lost to follow-up	1 (0.85)	0
Subject withdrew consent from follow-up	4 (3.42)	11 (9.24)
HR for study treatment (95% CI)	0.6802 (0.4921 to 0.9402)	
Two-sided p-value	0.0196	
Hazard ratio for change in therapy (95% CI)	1.0872 (0.7515 to 1.5728)	
Two-sided p-value	0.6574	

CI=confidence interval; HR=hazard ratio; OS=overall survival
Source: Company response to the ERG clarification letter, Table 12

Results from the Cox regression model with stepwise selection of covariates (p-value to enter <0.25, p-value to remain <0.15).are provided in Table 69 for OS.

Table 69 Overall survival Cox regression model including covariates in the NAPOLI-1 trial – ITT population

	Nal-iri+5-FU/LV (n=117)	5-FU/LV (n=119)
Excluded from analysis, n (%)	5 (4.27)	10 (8.40)
Died, n (%)	73 (62.39)	78 (65.55)
Censored, n (%)	39 (33.33)	31 (26.05)
HR (p-value) for other model selected terms		
Treatment group: nal-iri + 5-FU/LV	0.580 (0.0012)	
Baseline KPS ≥90	0.639 (0.0089)	
Baseline albumin ≥4 g/dL	0.697 (0.0305)	
Stage 4 at diagnosis	2.042 (0.0003)	
Time since last anti-cancer therapy >1.3 months	0.737 (0.0724)	
Presence of liver metastases	1.873 (0.0012)	
Baseline CA19-9 ≥40 U/mL	1.925 (0.0038)	
Age >65 years	1.338 (0.0781)	

HR=hazard ratio; KPS=Karnofsky performance score; OS=overall survival
Source: Company response to the ERG clarification letter, Table 13

11.6 Type of adverse events leading to dose modification in the NAPOLI-1 trial

11.6.1 Dose delay

The company highlights that the primary reasons for dose delay in the nal-iri+5-FU/LV arm were neutropenia and neutrophil count decreased (i.e. myelosuppression). From the company's CSR (Table 14.3.2.4.3), the ERG notes that neutropenia resulted in dose delay for [redacted] of patients in the nal-iri+5-FU/LV arm compared with [redacted] in the 5-FU/LV arm. Neutrophil count decreased resulted in dose delay for [redacted] and [redacted] respectively. Another notable AE resulting in dose delay in the nal-iri+5-FU/LV arm was [redacted] ([redacted] compared with [redacted] in the 5-FU/LV arm).

11.6.2 Dose reduction

Myelosuppression was also cited as the main reason for dose reduction with nal-iri+5-FU/LV, alongside gastrointestinal disorders. From the company's CSR (Table 14.3.2.4.1), most commonly (≥5%) [redacted] was a reason for [redacted] of cases in the nal-iri+5-FU/LV arm followed by [redacted].

11.6.3 Dose discontinuation

Gastrointestinal disorders and infections and infestations were the primary reasons cited by the company for discontinuation of treatment with nal-iri+5-FU/LV. As reported in Table 14.3.2.5.1 of the CSR, the proportions in the nal-iri+5-FU/LV arm for infections and infestations were [redacted] and [redacted] respectively.

11.7 Very common AEs reported in the NAPOLI-1 trial

The AEs that were very common (≥10%) in the NAPOLI-1 trial are summarised in Table 70.

Table 70 Summary of adverse events occurring in ≥10% of patients in any treatment group in the NAPOLI-1 trial – safety population

Adverse event, n (%)	Nal-iri (n=147)	Nal-iri+5-FU/LV (n=117)	5-FU/LV (n=134)
Any treatment emergent adverse event	145 (98.6)	116 (99.1)	132 (98.5)
Diarrhoea	103 (70.1)	69 (59.0)	35 (26.1)
Vomiting	80 (54.4)	61 (52.1)	35 (26.1)
Nausea	89 (60.5)	60 (51.3)	46 (34.3)
Decreased appetite	72 (49.0)	52 (44.4)	43 (32.1)
Fatigue	54 (36.7)	47 (40.2)	37 (27.6)
Anaemia	48 (32.7)	44 (37.6)	31 (23.1)
Abdominal pain	50 (34.0)	27 (23.1)	42 (31.3)
Pyrexia	29 (19.7)	27 (23.1)	15 (11.2)
Neutropenia	22 (15.0)	27 (23.1)	4 (3.0)
Constipation	26 (17.7)	26 (22.2)	32 (23.9)
Asthenia	35 (23.8)	24 (20.5)	22 (16.4)
Weight decreased	29 (19.7)	20 (17.1)	9 (6.7)
Neutrophil count decreased	15 (10.2)	17 (14.5)	2 (1.5)
White blood cell count decreased	10 (6.8)	17 (14.5)	2 (1.5)
Alopecia	32 (21.8)	16 (13.7)	6 (4.5)
Stomatitis	5 (3.4)	16 (13.7)	8 (6.0)
Dizziness	17 (11.6)	15 (12.8)	13 (9.7)
Back pain	12 (8.2)	15 (12.8)	16 (11.9)
Hypokalaemia	32 (21.8)	14 (12.0)	12 (9.0)
Oedema peripheral	28 (19.0)	13 (11.1)	20 (14.9)
Mucosal inflammation	8 (5.4)	12 (10.3)	5 (3.7)
Leukopenia	6 (4.1)	12 (10.3)	1 (0.7)
Platelet count decreased	3 (2.0)	12 (10.3)	3 (2.2)
Abdominal pain upper	17 (11.6)	11 (9.4)	10 (7.5)
Dehydration	15 (10.2)	9 (7.7)	9 (6.7)
Hypomagnesaemia	20 (13.6)	7 (6.0)	5 (3.7)
Hypoalbuminemia	19 (12.9)	7 (6.0)	8 (6.0)

Source: CS, adapted from Table 31

11.8 Non-randomised study of nal-iri monotherapy (NCT00813163)

The company also presents evidence in the CS from a multinational, single-arm phase 2 study of 40 patients treated with nal-iri monotherapy, referred to by its ClinicalTrials.Gov identifier, NCT00813163. This study was excluded from the company's systematic review since it did not include the intervention of interest, nal-iri+5-FU/LV.

Eligibility criteria for entry into the NCT00813163 study were not dissimilar to the NAPOLI-1 trial, the main exceptions being there was no specific stipulation that patients must have adequate renal function and patients were excluded if they had not been previously treated with irinotecan. Patients entered into the NCT00813163 study were also not permitted to have received prior irinotecan, whereas this was permitted in the NAPOLI-1 trial (under protocol version 2 or later), however the numbers of such patients were small ([redacted] patients in the nal-iri monotherapy arm and [redacted] patients in the nal-iri+5-FU/LV arm).

The nal-iri monotherapy dose and scheduling in the NCT00813163 study was the same as in the nal-iri monotherapy arm of the NAPOLI-1 trial. However, unlike the NAPOLI-1 trial, patients were not initially tested for the *UGT1A1*28* allele in the NCT00813163 study and so no initial dose reductions were made based on the results of any pharmacogenetic test in NCT00813163.

A descriptive critical appraisal of the only included non-randomised study was undertaken using a tool developed by Chambers 2009.[63] This includes eight items and for a study to be considered 'good' quality, all eight criteria must be met. The NCT00813163 study met five of the criteria including one or more of the criteria deemed by Chambers 2009 to classify the study as 'satisfactory' quality. The ERG considers that this checklist for assessing the quality of the non-randomised study appears to be an appropriate tool but the ERG notes that while it has been used in a modified format in three systematic reviews,[64-66] it has not been validated as a tool. Indeed, one of the future research recommendations of Chambers 2009 was to focus on focus on validating quality criteria.

Some notable baseline differences between the NCT00813163 study and the NAPOLI-1 trial were differences in the proportion of Asian patients, male patients, baseline KPS and patients previously treated with gemcitabine monotherapy or combination therapy as summarised in Table 71.

Table 71 Notable differences in baseline characteristics between the NCT00813163 study and nal-iri arms of the NAPOLI-1 trial*

Baseline characteristic	NCT00813163	NAPOLI-1	
	Nal-iri (n=40)	Nal-iri (n=151)	Nal-iri + 5-FU/LV (n=117)
Male, n (%)	19 (47.5)	87 (57.6)	69 (59.0)
Asian	25 (62.5)	52 (34.4)	34 (29.1)
KPS ≤70	10 (25.0)	15 (9.9)	10 (8.5)
Previously treated with gemcitabine monotherapy	9 (22.5)	67 (44.3)	53 (45.3)
Previously treated with gemcitabine combination	31 (77.5)	84 (55.6)	64 (54.7)

*For the NAPOLI-1 trial, data are for ITT population
Source: CS, adapted from Tables 14 and 28 and Wang-Gillam 2015 paper

In the NCT00813163 study, the primary endpoint was OS rate at 3-months with additional secondary endpoints including (but not limited to) PFS and ORR. Overall, key efficacy results appear to be similar to those reported in the NAPOLI-1 trial (Table 72).

Table 72 Key findings from the NCT00813163 study and NAPOLI-1 trial*

Outcome	NCT00813163	NAPOLI-1	
	Nal-iri (n=40)	Nal-iri (n=151)	Nal-iri+5-FU/LV (n=117)
Median OS (95% confidence interval)	5.2 (--, --)	4.9 (4.2, 5.6)	6.1 (4.76, 8.87)
Proportion of patients alive at:			
• 3 months, n (%)	30 (75.0)	--	--
• 6 months, n (%)	17 (42.5)	--	--
• 12 months, n (%)	10 (25.0)	--	30 (25.6)
Median PFS (95% confidence interval)	2.4 (--, --)	2.7 (2.1, 2.9)	3.1 (2.69, 4.17)
Objective response rate, n (%)	3 (7.5)	9 (6.0)	9 (7.7)

OS=overall survival; PFS=progression-free survival
-- Not reported
*For the NAPOLI-1 trial, analyses are for ITT population, median OS and median PFS are the Kaplan-Meier estimate of the median PFS time
Source: CS, executive summary and adapted from Tables 16, 18, 22 and 29 and Wang-Gillam 2015 paper

Safety data, in particular, from this study does however add supporting evidence for toxicity associated with nal-iri. A total of 27 patients (67.5%) were able to maintain a dose of 120 mg/m^2 throughout their entire treatment course in the NCT00813163 study, and the majority of patients (75.0%) discontinued due to disease progression rather than toxicity. In the NAPOLI-1 trial, the company noted that certain gastrointestinal AEs and alopecia, hypoalbuminemia, hypomagnesaemia, hypokalaemia and asthenia were more commonly reported in the nal-iri monotherapy arm, while myelosuppression and stomatitis were more common in the nal-iri+5-FU/LV arm. The frequency of severe TEAEs (Grade 3 or higher) was generally also higher in the nal-iri monotherapy arm than nal-iri + 5-FU arm (with the exception of neutropenia, white cell count decreased, neutrophil count decreased, and fatigue). This, the company argues, suggests that the more frequent administration of nal-iri

(every 2 weeks compared with every 3 weeks) with a lower dose, as in the nal-iri+5-FU/LV combination arm compared with the nal-iri monotherapy arm, results in fewer and less severe gastrointestinal AEs. Clinical advice to the ERG is that a similar pattern is observed with treatment with non-liposomal irinotecan monotherapy and FOFIRI.

There were notable differences in the incidence of AEs in the NCT00813163 study and the NAPOLI-1 trial when only the nal-iri monotherapy arms were compared. In particular, in the NCT00813163 study there was an increase in the incidence of the following AEs when compared with AE data from the nal-iri monotherapy arm of NAPOLI-1 trial (Table 73): leukopenia (+33.1%), fatigue (+26.2%), neutropenia (+25.0%), alopecia (+20.3%) and 'weight decreased' (+18.8%). There was an increase in the incidence of the following grade ≥3 AEs when compared with AE data from the nal-iri monotherapy arm of NAPOLI-1 trial (Table 74): neutropenia (+24.6%) and leukopaenia (+22.3%). Possible explanations for these differences between studies include differences in the baseline characteristics, particularly the greater proportion of Asians, patients with KPS ≤70 and previous use of gemcitabine combination therapy in the NCT00813163 study than in the NAPOLI-1 trial. The fact that patients were not tested for *UGT1A1*28* prior to receiving treatment in NCT00813163 may also have been a factor although the authors of the non-randomised study note there was no correlation between *UGT1A1* polymorphisms with either haematologic AEs (myelosuppression) or non-haematologic AEs (including gastrointestinal disorders). The sample size of the NCT00813163 study was also relatively small and this could also explain why some AEs appear to be more common in this study than in the NAPOLI-1 trial.

Table 73 Adverse events occurring in ≥10% of subjects in NCT00813163 and a comparison of the incidence of the same adverse events in the NAPOLI-1 trial*

Adverse Event n (%)	NCT00813163	NAPOLI-1	
	Nal-iri (n=40)	Nal-iri (n=147)	Nal-iri + 5-FU/LV (n=117)
Diarrhoea	30 (75.0)	103 (70.1)	69 (59.0)
Fatigue	25 (62.5)	54 (36.7)	47 (40.2)
Nausea	24 (60.0)	89 (60.5)	60 (51.3)
Vomiting	23 (57.5)	80 (54.4)	61 (52.1)
Anorexia / decreased appetite†	23 (57.5)	72 (49.0)	52 (44.4)
Alopecia	17 (42.5)	32 (21.8)	16 (13.7)
Neutropenia	16 (40.0)	22 (15.0)	27 (23.1)
Abdominal pain	15 (37.5)	50 (34.0)	27 (23.1)
Weight decreased	15 (37.5)	29 (19.7)	20 (17.1)
Leukopenia	15 (37.5)	6 (4.1)	12 (10.3)
Anaemia	13 (32.5)	48 (32.7)	44 (37.6)

*For the NAPOLI-1 trial, analyses are for the safety population
† Reported as anorexia in the NCT00813163 study and decreased appetite in the NAPOLI-1 trial
Source: CS, Table 31 and Table 32

Table 74 Adverse events of grade 3 or higher occurring in ≥10% of subjects in the NCT00813163 study and the NAPOLI-1 trial*

Adverse Event n (%)	NCT00813163	NAPOLI-1	
	Nal-iri (n=40)	Nal-iri (n=147)	Nal-iri + 5-FU/LV (n=117)
Any treatment-emergent adverse event ≥grade 3	26 (65.0)	112 (76.2)	90 (76.9)
Neutropenia	12 (30.0)	8 (5.4)	17 (14.5)
Leukopenia	10 (25.0)	4 (2.7)	1 (0.9)
Fatigue/asthenia†	8 (20.0)	19 (12.9)	28 (23.9)
Diarrhoea	6 (15.0)	31 (21.1)	15 (12.8)
Anaemia	6 (15.0)	16 (10.9)	11 (9.4)
Abdominal pain	6 (15.0)	12 (8.2)	8 (6.8)
Hyponatraemia	6 (15.0)	9 (6.1)	3 (2.6)
Gamma-glutamyl transferase elevated	5 (12.5)	--	--
Nausea	4 (10.0)	20 (13.6)	13 (11.1)
Anorexia	4 (10.0)	--	--

*For the NAPOLI-1 trial, analyses are for the safety population
†Data reported for fatigue/asthenia combined in the NCT00813163 study but reported separately for the NAPOLI-1 trial; hence for the NAPOLI-1 trial the data have been combined by adding the two categories together in this table

11.9 Survival modelling: ERG survival extrapolation

Overall survival in the 5-FU/LV arm of the NAPOLI-1 trial was extrapolated using a simple 2-parameter exponential model fitted to the K-M events occurring between 11.3 and 34 months. The last event at 34.9 months was excluded as too unstable (95% confidence interval includes zero).

The following exponential function was applied to the 5-FU/LV arm from 28.4 months onwards:

OS = EXP(-(0.063822 * months + 1.2008081))

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11.10 ERG changes to submitted company model

All revisions are activated by a logic switch with 0 = unchanged, 1 = apply ERG modification

Logic switches are indicated by range variables Mod_n = 1 – 13

A menu of revisions/Mod numbers appears on the 'CEA' worksheet together with summary results as used to transfer to the ERG report.

Model Revision	Binary Switch	Sheet	Implementation Instructions
Table 25-R1. 5-FU/LV Pre-progression time on treatment curve for oxaliplatin+5-FU/V dosing curve	Mod_11	Log-normal	Replace formula in cell AB12 by =IF(Mod_12=0,(MIN(1-NORM.S.DIST((LN($Q12*84/365.25)-P_3231)/P_3232, TRUE),AD12)),(MIN(1-NORM.S.DIST((LN($Q12*84/365.25)-P_3131)/P_3132, TRUE),T12))) copy formula in cell AB12 to range AB13:AB533
Table 27-R1. ERG OS naliri+5-FUV/LV	Mod_2	Log-normal	Replace formula in cell Z12 by =IF(Mod_2=0,(1-NORM.S.DIST((LN($Q12*84/365.25)-P_3221)/P_3222, TRUE)),'ERG OS'!W5) copy formula in cell Z12 to range Z13:Z533
Table 27-R1. ERG PFS naliri+5-FUV/LV	Mod_2	Log-normal	Replace formula in cell Y12 by =IF(Mod_2=0,(1-NORM.S.DIST((LN($Q12*84/365.25)-P_3211)/P_3212, TRUE)),'ERG OS'!AC5) copy formula in cell Y12 to range Y13:Y533
Table 27-R1. ERG pre-progression on treatment nal-iri+5-FUV/LV	Mod_2	Log-normal	Replace formula in cell W12 by =IF(Mod_2=0,(MIN(1-NORM.S.DIST((LN($Q12*84/365.25)-P_3231)/P_3232, TRUE),Y12)),'ERG OS'!AF5) copy formula in cell W12 to range W13:W533
Table 27-R1. ERG OS 5-FUV/LV	Mod_2	Log-normal	Replace formula in cell U12 by =IF(Mod_2=0,(1-NORM.S.DIST((LN($Q12*84/365.25)-P_3121)/P_3122, TRUE)),'ERG OS'!AA5) copy formula in cell U12 to range U13:U533
Table 27-R1. ERG PFS 5-FUV/LV	Mod_2	Log-normal	Replace formula in cell T12 by =IF(Mod_2=0,(1-NORM.S.DIST((LN($Q12*84/365.25)-P_3111)/P_3112, TRUE)),'ERG OS'!AD5) copy formula in cell T12 to range T13:T533
Table 27-R1. ERG pre-progression on treatment 5-FUV/LV	Mod_2	Log-normal	Replace formula in cell R12 by =IF(Mod_2=0,(MIN(1-NORM.S.DIST((LN($Q12*84/365.25)-P_3131)/P_3132, TRUE),T12)),'ERG OS'!AG5) copy formula in cell R12 to range R13:R533
R2. Full dose intensity 5-FU/LV	Mod_3	Control	Replace formula in cell I18 by =IF(Mod_3=0,95%,100%) Replace formula in cell J18 by =IF(Mod_3=0,95%,100%)
R2. Full dose intensity Nal-iri+5-FU/LV	Mod_3	Control	Replace formula in cell C18 by =IF(Mod_3=0,85%,100%) Replace formula in cell D18 by =IF(Mod_3=0,85%,100%) Replace formula in cell E18 by =IF(Mod_3=0,85%,100%)
R2. Full dose	Mod_3	Control	Replace formula in cell F18 by =IF(Mod_3=0,85%,100%)

Model Revision	Binary Switch	Sheet	Implementation Instructions
intensity Oxaliplatin+ 5-FU/LV			Replace formula in cell G18 by =IF(Mod_3=0,85%,100%) Replace formula in cell H18 by =IF(Mod_3=0,85%,100%)
R2. Full dose intensity 5-FU/LV	Mod_3	Input - Cost	Replace formula in cell E9 by =Control!I18 Replace formula in cell F9 by =Control!J18
R2. Full dose intensity Nal-iri+5-FU/LV	Mod_3	Input - Cost	Replace formula in cell H9 by =Control!C18 Replace formula in cell I9 by =Control!D18 Replace formula in cell J9 by =Control!E18
R2. Full dose intensity Oxaliplatin+ 5-FU/LV	Mod_3	Input - Cost	Replace formula in cell L9 by =Control!F18 Replace formula in cell M9 by =Control!G18 Replace formula in cell N9 by =Control!H18
R3. ERG BSA	Mod_5	Control	Replace formula in cell C8 by =IF(Mod_5=0,1.79,1.795)
R3. ERG BSA	Mod_5	Control	Replace formula in cell D8 by =IF(Mod_5=0,1.79,1.795)
R3. ERG BSA	Mod_5	Parameters	Replace formula in cell D10 by =Control!C8 OR Replace formula in cell D10 by =Control!D8
R4. ERG drug acquisition costs 5-FU/LV	Mod_4	Input – Cost	Replace formula in cell E19 by =IF(AND(Mod_4=0,Mod_3=1),E18+F8,0)+(IF(AND(Mod_4=1,Mod_3=1),Control!X16,0)+ IF(AND(Mod_4=1,Mod_3=0),Control!X16,0)+IF(AND(Mod_4=0,Mod_3=0),E18+F18,0))
R4. ERG drug acquisition costs nal-iri+5-FU/LV	Mod_4	Input – Cost	Replace formula in cell H19 by =IF(AND(Mod_4=0,Mod_3=1),H18+I18+J18,0)+(IF(AND(Mod_4=1,Mod_3=1),Control!R16,0)+ IF(AND(Mod_4=1,Mod_3=0),Control!R16,0)+IF(AND(Mod_4=0,Mod_3=0),H18+I18+J18,0))
R4. ERG drug acquisition costs oxaliplatin+5-FU/LV	Mod_4	Input – Cost	Replace formula in cell L19 by =IF(AND(Mod_4=0,Mod_3=1),L18+M18+N18,0)+(IF(AND(Mod_4=1,Mod_3=1),Control!U16,0)+ IF(AND(Mod_4=1,Mod_3=0),Control!U16,0)+IF(AND(Mod_4=0,Mod_3=0),L18+M18+N18,0))
R5. ERG Post progression	Mod_6	Input - Cost	Replace formula in cell BV9 by =IF(Mod_6=0,62%,100%)

Model Revision	Binary Switch	Sheet	Implementation Instructions
costs 5-FU/LV			
R5. ERG Post progression costs nal-iri+5-FU/LV and oxaliplatin+5-FU/LV	Mod_6	Input - Cost	Replace formula in cell BW9 by =IF(Mod_6=0,69%,100%)
R5. ERG Post progression costs 5-FU/LV	Mod_6	Input - Cost	Replace formula in cell CL9 by =IF(Mod_6=0,CL7*CL8,0)
R5. ERG Post progression costs nal-iri+5-FU/LV	Mod_6	Input - Cost	Replace formula in cell CM9 by =IF(Mod_6=0,CM7*CM8,0)
R5. ERG Post progression costs oxaliplatin+5-FU/LV	Mod_6	Input - Cost	Replace formula in cell CN9 by =IF(Mod_6=0,CN7*CN8,0)
R6. ERG health state utilities (pre-progression)	Mod_1	Parameters	Replace formula in cell D110 by =IF(Mod_1=0,0.742,0.671)
R6. ERG health state utilities (post-progression)	Mod_1	Parameters	Replace formula in cell D111 by =IF(Mod_1=0,0.671,0.6)
R7. ERG terminal disutility 5-FU/LV	Mod_10	Input – Utility	Replace formula in cell C12 by =IF(Mod_10=0,Parameters!$D$111,Parameters!$D$111-J20)
R7. ERG terminal disutility nal-iri+5-FU/LV	Mod_10	Input – Utility	Replace formula in cell D12 by =IF(Mod_10=0,Parameters!$D$111,Parameters!$D$111-J20)
R7. ERG terminal disutility oxiplatin+5-FU/LV	Mod_10	Input – Utility	Replace formula in cell E12 by =IF(Mod_10=0,Parameters!$D$111,Parameters!$D$111-J20)
Minor Issues	**Binary Switch**	**Sheet**	**Implementation Instructions**
ERG 5-FU dose	Mod_13	Input – Cost	Replace formula in cell M8 by =IF(Mod_13=0,1000,2400)
ERG 5-FU dose	Mod_13	Control	Replace formula in cell G16 by =IF(Mod_13=0,1000,2400)
Terminal Care Costs	Mod_7	Input - Cost	Replace formula in cell CH9 by =IF(Mod_7=0,(CH7+CH8),terminalcostERG)
Pharmacist costs	Mod_8	Input – Cost	Replace formula in cell E13 by =IF(Mod_8=0,E7*E11*E12,E7*E11*E12+11) Replace formula in cell I13 by =IF(Mod_8=0,I7*I11*I12,I7*I11*I12+11)

Model Revision	Binary Switch	Sheet	Implementation Instructions
			Replace formula in cell M13 by =IF(Mod_8=0,M7*M11*M12,M7*M11*M12+11)
Pharmacist costs	Mod_8	Control	Replace formula in cell S9 by =IF(Mod_8=0,admincost_n5L_5FU,admincost_n5L_5FU+11) Replace formula in cell V9 by =IF(Mod_8=0,admincost_o5L_5FU,admincost_o5L_5FU+11) Replace formula in cell X9 by =IF(Mod_8=0,admincost_5L_5FU,admincost_5L_5FU+11)
Infusion disconnection costs (Nurse visit)	Mod_9	Input - Cost	Replace formula in cell AD8 by =IF(Mod_9=1,Parameters!$D$42*0.5+nurse90,Parameters!$D$42*0.5+Parameters!$D$43) Replace formula in cell AG8 by =IF(Mod_9=1,Parameters!$D$42*0.5+nurse90,Parameters!$D$42*0.5+Parameters!$D$43) Replace formula in cell AJ8 by =IF(Mod_9=1,Parameters!$D$42*0.5+nurse90,Parameters!$D$42*0.5+Parameters!$D$43)
ERG Adverse event costs	Mod_12	Input – Cost	Replace formula in cell A07 by =IF(Mod_12=0,Anaemia,405.47) Replace formula in cell AO9 by =IF(Mod_12=0,AbdominalPain,752.1) Replace formula in cell AO10 by =IF(Mod_12=0,Diarrhoea,2739.9) Replace formula in cell AO11 by =IF(Mod_12=0,Nausea,2739.9) Replace formula in cell AO12 by =IF(Mod_12=0,Vomiting,2739.9) Replace formula in cell AO13 by =IF(Mod_12=0,Fatigue,1848)